Medical Library NOV 13 1930

VOLUME 14 NUMBER 4

ENDOCRINOLOGY

THE BULLETIN OF THE ASSOCIATION
FOR THE STUDY OF

INTERNAL SECRETIONS

EDITORS

R. G. HOSKINS, Boston

M. O. LEE, Boston H. LISSER, San Francisco

JULY-AUGUST

1930

PUBLISHED BI-MONTHLY BY THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS, SUITE 1214 WILSHIRE MEDICAL BLDG., LOS ANGELES, CALIFORNIA
ANNUAL SUBSCRIPTION, $6.00 SINGLE COPIES, $1.25

At the Menopause

The distressing symptoms that so often accompany the climacteric, but more particularly the aggravated symptoms of the artificial menopause, are frequently controlled by the administration of

LUTEIN TABLETS, H. W. & D.
LUTEIN SOLUTION AMPULES, H. W. & D.

The choice of the medication depends, of course, on the judgment of the physician as to whether oral or hypodermatic administration is indicated. Both products represent the

CORPUS LUTEUM OF THE SOW

Lutein Tablets H. W. & D. are unmodified by treatment with solvents or by exposure to temperatures above animal body heat in the drying process. All separation of extraneous matter is made by mechanical means and all drying is in vacuo. The unaltered corpus luteum should, therefore, be presented in our products and clinical experience with them should demonstrate their therapeutic activity.

Ovarian dysfunction as evidenced in dysmenorrhea and amenorrhea is also an indication for Lutein medication. Where the diagnosis of such dysfunction was well established, definite therapeutic results have been reported.

WHOLE OVARY TABLETS, H. W. & D.
OVARIAN RESIDUE TABLETS, H. W. & D.

are also offered for those who prefer, for certain indications, the use of the whole gland or of the residue remaining after corpus luteum separation.

Literature furnished on request

H. W. & D.—SPECIFY—H. W. & D.—SPECIFY—H. W. D. SPECIFY—H. W. & D.

HYNSON, WESTCOTT & DUNNING

BALTIMORE, MD.

ENDOCRINOLOGY

THE BULLETIN OF THE ASSOCIATION FOR THE STUDY OF

INTERNAL SECRETIONS

Volume 14, Number 4 JULY-AUGUST, 1930 Serial No. 72

NEW CONCEPTS CONCERNING THE PATHOGENESIS OF OBESITY AND THE PROBLEMS OF BASAL METABOLISM*

DR. HERMANN BERNHARDT

Assistant of The Clinic

Privatdozent of The University of Berlin.

Whoever is interested in the study of obesity will know the standard work of Carl von Noorden on this subject. It was in 1910 that his book upon obesity appeared for the second and last time. The problems of obesity seemed to be settled.

As to the etiology and pathogenesis of obesity von Noorden believed in the important influence of the thyroid and he thought that most of the cases of obesity are due to a hypofunction of this gland. Von Noorden was the first clinician to carry out a strict analysis of the total metabolism of a patient. He partly based his conceptions on the fundamental studies of Magnus-Levy. Von Noorden pointed out that the total daily metabolism of a person can be considered as compounded from three principal factors:

(1) The basal metabolism: By this term is meant the heat-production when the body is at complete rest and at a sufficient time after a meal to escape the stimulative effect of food. As a rule, twelve to fifteen hours must be passed after the last meal, and a rest of 1-1½ hours must be strictly observed before the beginning of the examination. The basal metabolism of the adult is approximately 960 calories per day per square meter of skin surface. The surface area of an individual may be estimated conveniently from the weight and height by means of a formula devised by E. F. and D. Du Bois.

$$A = W^{0.425} \times H^{0.725} \times 71.84.$$

W=weight in kgm.
H=height in cm.
71.84=constant amount (C).

With advancing age there is a slight falling off in metabolism, while in infancy and childhood there is a notable increase.

*From the First Medical Clinic of The University of Berlin (Charité), (Direktor: Geheimrat Prof. Dr. W. His).

*Read at the Fourteenth Annual Meeting of the Association for the Study of Internal Secretions, Detroit, June 24, 1930.

(2) The second factor is the amount of energy necessary for the muscular work during the day. Naturally, this depends on the amount and the kind of muscular work carried out. Van Noorden calculated the amount for a normal man at light work 840 calories daily and he considered from this number 250 calories as the amount corresponding to the real effect of the work done, 590 calories as the amount for the surplus production of heat in the body, as the human body does not work with the positive measurable efficiency of 100 per cent.

(3) The third factor is the surplus production of heat that results as a reaction to the intake of nourishment. This factor is the smallest and von Noorden calculated about 200 calories per day at the ordinary diet. Von Noorden was of the opinion that this surplus production of heat was due to the work that the stomach, the intestine, and the liver had to do shortly after the intake of food. But later investigations, especially by Rubner and his co-workers, showed that this cannot be the first factor. Fat and oil can be taken in rather large amounts without any noticeable increase in the metabolic rate during the next hours. Carbohydrates show some increase but mostly not very marked. Only the proteins are apt to produce an evident increase in metabolism and this increase occurs so soon after the intake of food that a nervous reaction must play the first role. Rubner was the first to study these problems extensively: he called the increase in the metabolic rate "specific dynamic action of food" (Spezifisch-dynamische Wirkung der Nahrung).

The addition of these three factors gives the total sum of the daily metabolic rate of a person. It is clear that the whole metabolism will keep its balance in case that the calories of the daily nourishment correspond to the total amount. Should I keep a normal person out of bed with light muscular work and should I give to this person a nourishment only equal to the basal metabolic rate found in this person, the person would show a negative balance of energy and would lose in weight. Naturally the water and salt intake has to be observed very thoroughly during these experiments. This can easily be done by giving only 700 to 800 cc. of fluid and 5 to 7 gm. of salt daily. I have made such experiments in a series of normal persons and I always found a marked loss of weight when I put them on a diet equal only to their own basal metabolic rate. So one can say that the analysis of von Noorden proved to be right in these normal persons.

Von Noorden, however, claimed that this way to find the total amount of the daily heat production by the addition of the three factors mentioned above had to be used under pathological conditions. All three factors are of importance in this regard and must be studied in the different diseases.

The basal metabolism was studied in a large number of cases of nearly all diseases throughout the whole world. An immense literature exists at the present time upon this problem. Marked differences could only be found in cases of disturbances of the thyroid gland. Friedrich

von Müller and Magnus-Levy were the first to point out this important fact. Slight changes of the basal metabolic rate were found under many conditions. I only wish to mention the slight increase in cases of severe anemia, of hypertonia, of diabetes melitus showing acidosis, of leukemia, etc. Naturally all conditions with increased temperature of the body show increased metabolic rate. Decreased basal metabolism was found in all cases of under-nourishment, in cases of pituitary and pluriglandular cachexia, of advanced Addison's disease, and of nephrosis, especially lipoid nephrosis. It is impossible for me to cover this question here completely. As to the clinical standpoint the basal metabolism proved to be of interest and of importance rather only in the cases of thyroid disturbances. Hypothyroidism shows marked decrease of the metabolic rate whereas hyperthyroidism is combined with a notable increase. These facts are of leading importance as to the diagnostic work.

It is very interesting to state that the patients with obesity show in about 66 per cent a basal metabolic rate within the normal limits. In about 25 per cent one even finds a high rate and only in about 10 per cent of the cases a more or less marked decrease could be noted. These numbers are based on my own investigations carried out on more than 100 subjects of obesity of all kinds. The fact that obese people show, as a rule, a normal basal metabolism has also been stated by other investigators. I mention A. Loewy, Hausleiter, Kestner, and his assistants, Grafe, Lauter, Strouse, Wang, Means, Minnig, McCaskey and Eidelsberger.

As to the second factor, the surplus energy due to the muscular work, I wish to mention the investigations that H. Gessler (Heidelberg, Germany), published some years ago. He studied the heat production of normal and of obese people doing the same muscular work and found a rather marked difference, obese people showing 20 per cent less increase during the work than normal people. Unfortunately, other investigators (S. Lauter, S. Strouse) and myself could not confirm these results. Obese people show, as a rule, the same increase of metabolic rate during muscular work as normal people. On the contrary, when forced to heavy work they show a higher increase and mostly a longer lasting increase than normal people as S. Lauter and myself could state. As to the period following muscular work, I shall speak about this later on more extensively.

The third factor, the specific dynamic action of food, especially of proteins, has been studied in obese people by many authors. Jaquet and Svenson were the first to state that there is mostly a marked difference between healthy people and obese persons, the specific dynamic action of food being smaller in the obese. Many authors could establish this fact: G. von Bergmann, Staehelin, Rolly, Kestner, Plaut, Liebesny, Knipping, Dürr, Biedl, Strouse, and so on. My own investigations showed the same, but it must be stated that sometimes also a normal specific dynamic action can be found, especially in cases that offer symptoms of hypofunction of the gonads. But even if one would suppose this third factor

being only one-fourth of the normal it would not be possible to base the pathogenesis of obesity on that point alone.

The work I have carried out on obesity since 1923 showed that the critical point lies indeed in another line. I desired to study the importance of the basal metabolic rate found in obese people. I did it by keeping the obese for three to four weeks and longer on a diet that was in its caloric amount equal to the amount of the basal metabolism of these patients. I laid stress on the fact that these patients performed light muscular work, mostly by walking around for a certain time during the day. I am of the opinion that we do not deal with normal and comparable conditions if we would keep our patients submitted to these experiments in bed for all twenty-four hours of the day. The light muscular work that all normal people carry out every day plays such an important role in the balance of the daily metabolism that we get other than normal conditions when we omit this factor totally. I wish to quote the old German proverb: "Das Bett zehrt", which means, lying in bed for a long time without any muscular exercise one will lose very soon in weight and strength. It is obvious that the factor of inactivity plays a large role in this condition.

The patients who were held on that strict diet equal to their own basal metabolic rate were kept under rigorous observation. The fluid intake was restricted to 700 to 800 cc. and the amount of salt did not exceed 7 gm. daily so that there was no possibility of retention of water or salt. It was very interesting to state that nevertheless nearly all patients that showed endogenous obesity did not lose in weight during this diet. Some of them even gained weight noticeably. These experiments were repeated with the utmost accuracy and today I can state with absolute conviction that most of the patients with endogenous obesity, if held on a diet equal to their own basal metabolic rate, even for weeks, will not lose in weight but may sometimes even gain in weight during this period.

These results made evident the fact that in these obese people the analysis of metabolism given by Von Noorden did not hold, for if it would prove correct, the obese patients should show marked loss of weight during this strict diet. On the other hand, S. Lauter and myself have found that during muscular work the metabolic rate increases in about the same amount in obese as in normal persons. The results of these two investigations seem to be in sharp contrast. After repeated attempts I succeeded in analyzing the whole problem. I could state by taking the metabolic rate of these patients with only very short intervals during the whole day that there are periods where the metabolic rate is markedly less than that taken in the morning. I call these periods of decreased metabolic rate "negative phases" (negative Phasen). They occur most noticeably in the time following light muscular work but also very often after the intake of food. In this case you will find at first a short period of slight increase of the metabolic rate followed later on by

a longer period of marked decrease. These negative phases also occur during sleep (Talbot's case). It is very important to state that all the negative phases as a rule, last longer than one or two hours so that the caloric effect is very important. If one estimates on one side all the positive phases of metabolism and on the other side all the negative phases in obese persons for twenty-four hours, one very often comes to the result that the negative phases are so marked that they balance the positive ones. In this way a total sum of the daily heat-production results that is very near to the basal metabolic rate, in some cases it is even smaller than this amount. One gets an idea of the results more clearly when one draws a curve according to the series of findings during twenty-four hours. The basal metabolic rate is taken as the horizontal axis so that the positive phases are above the line and the negative phases beneath. It is very easy to get the balance of the positive and negative sums by a mathematical formula. Also simple geometrical comparation is possible.

That there are obese people who keep their weight under a very strict diet taken even for a long time has been observed by many authors before me, but it was only a mere statement of facts. No analysis was given. Von Noorden himself reports in his book some of these cases. Very interesting is his report of a man aged thirty-nine years, who weighed 102 kgm. This man was kept for three months on a diet of 1720 calories or less and though he exercised daily in the open air he did not lose more than 1 kgm. weight. Von Noorden estimates his actual caloric requirements at about 2700 calories daily. A control subject weighing 98 kgm. exercising less actively lost nearly 5 kgm. in four weeks on the same diet. Schwenkenbecher, Salomon, A. Loewy and F. Hirschfeld, Grafe, Umber, Düring, Talbot, Plaut and Strouse reported similar cases. The conclusions, if drawn, varied. Strouse, for instance, stated that persons showing the predisposition of so-called constitutional obesity show no interdependence between food intake, energy expense and weight. Dietary studies proved that certain types of obese persons maintain their weight without regard to the usually accepted caloric balance. In a second paper he comes to the conclusion that neither excessive underweight nor excessive overweight is associated with a constant change in basal metabolism. "Obesity cannot be caused by changes in the basal metabolism."

Out of my own observations I wish to mention a patient of thirty-four years of age, 156 cm. in height, and 83 kgm. in weight. As this patient was very eager to lose weight she remained under strict observation for a long period. Her basal metabolic rate was taken nearly every day and proved to be very constant: 1750 calories. Her diet was fixed at this amount. During an observation of three months this patient gained 1.5 kgm. It was very interesting to observe that the weight showed a relation to the menstruation. The highest weight was always found just before the beginning of the menstruation. Besides this she complained of severe headache during the week before the period. During menstruation the headaches disappeared and a slight decrease of weight was observed. It is

important to say that the patient was always held at 800 cc. of fluid and at less than 7 gm. of salt daily. Later on her diet was restricted to a milk diet of Karrel (800 cc. of milk). This is equal to about 600 calories. Under this diet the patient showed loss of weight, about 0.8 to 1 kgm. a week. The analysis of metabolism in this patient proved that she showed very long but not very deep negative phases and that the daily metabolic rate had to be considered as smaller than the basal metabolic rate taken in the morning.

The factor of the negative phases, especially after light muscular work, is also apt to elucidate those cases of obesity, where keeping at rest proved more efficient as to the loss of weight, than light muscular work. G. Leven, in 1904, reported the history of a patient of 108 kgm. who had sold his car and walked to his office every morning in order to lose in weight. But he did not lose at all, although his diet was very strict. However, Leven succeeded in having him lose some weight by applying a rest therapy to him without changing his diet.

Normal persons, as a rule, show no negative phases during the day, but there is no doubt that by and by more conditions of that kind will be found and that there are transitions from obese people to the normals. One can prove it by the fact that one can hold a normal person at the same condition as to the muscular work and can alter the nourishment to a rather large amount without a change of weight. Grafe and Koch demonstrated this extensively.

It is very interesting, as I determined, that also in normal persons these negative phases occur when there are conditions that require highest economy of energy. A very good example is the analysis of the metabolism of convalescents who make a rapid gain in weight. They show, as a rule, a perfectly normal, even a high basal metabolic rate, but show after light muscular work marked negative phases. Mostly these phases are shown also after the intake of food. It will be very important to study the different diseases as regards this problem of the relation of the basal metabolic rate to the whole heat-production during twenty-four hours. It is clear that our view and idea about the basal metabolic rate must be altered, and that the term "basal metabolism" is no longer to be regarded as apposite. This term is a translation of the German expression, "Grundumsatz," that was introduced by A. Magnus-Levy. This metabolic rate can no longer be considered as characteristic of the whole day's metabolism. In German I have suggested the simple descriptive term, *"Ruhenüchternumsatz,"* and in English I would say, *"standard metabolism"* (Krogh, E. F. DuBois).

As to the clinical aspect of obesity the studies made during the last twenty years are closely connected with the investigations of endocrinology. Soon after it was stated that the function of almost all endocrine glands is important for certain processes of metabolism, the problem of obesity as an endocrine disturbance was started. It is very interesting to follow this development. Nowadays we can say that there is no endocrine gland that was not accused by some authors of being the cause of obesity.

A gross discrepancy arose and the clinic tried to get its best out of the different theories.

As to the routine procedure the history of the patients mostly gives the best help, especially as to the question whether we deal with exogenous obesity caused by overeating and inactivity or with an endogenous obesity. Besides this, the physical examination with special reference to endocrine signs, fat distribution, hair, teeth, skin, sex organs, measurements, etc., is important. X-ray pictures of the sella turcica, sugar tolerance skiagrams of the thymus region, basal metabolic and blood chemistry studies are added. The cases of endogenous or endocrinopathic obesity are divided according to the endocrine symptoms found mostly along the following division:

(1) Pituitary disease (Froehlich's disease, dystrophia adiposo-genitalis) as evidenced by girdle obesity, small sella turcica, delayed menses or amenorrhea, deficient sex organs, disturbances of the water and salt metabolism.

(2) Thyroid disease, present or absent struma, low basal metabolism, slow pulse rate, myxedematous infiltration, etc.

(3) Thymic origin: type, low blood pressure, vagotonia, positive thymus shadow.

(4) Pre-diabetic type.

(5) Gonadal type: trochanteric obesity, menopause.

(6) Mixed type: pluriglandular type.

(7) Very seldom pineal origin, adrenal origin, and pancreatic origin.

Besides this there is a group of unexplained endogenous obesities that is mostly called idiopathic obesity where no special endocrine symptoms are found. Lipomatosis and Dercum's disease may be left aside as they show so many symptoms that lie outside the realm of obesity.

This clinical division is used in nearly all clinics of the United States as I found by observation and from the voluminous literature.

I cannot deal extensively with the different factors of routine procedure in obesity. However, I wish to mention that we should lay more stress on the respiratory quotient: the ratio CO_2:O_2. If this quotient shows a high value, near 1.0 or even over 1.0, we deal with a case of obesity that presents a marked tendency to saving his fat tissues and to synthesizing carbohydrates to form fat. Most of the patients with pituitary or cerebral obesity offer this phenomenon. Clinically, it is of importance as it indicates that it will be very difficult to get these patients to use their own fat tissues. Especially when a normal or high metabolic rate is found the difficulty of producing fat decomposition is rather insurmountable. On the other hand, a low respiratory quotient gives a good clinical prognosis as the fat decomposition is preferred. During the period of losing weight all obese show normal or low respiratory quotients.

That the water- and salt-metabolism must be observed in all cases of obesity is a well-known fact. This factor can be so important that it outdoes all others and that one gets no therapeutic results before taking account of it. But on the other hand, it must be stated that the theory that there is always a hydrophile factor in obesity and that the fat tissues contain more water than normal tissues does not hold. I only mention Foster and Benninghoven, who found that the fat tissues of their rats brought experimentally to marked obesity, was very poor in water and that the fat rats as a whole showed much less water in their body than the control animals. It is a well-known fact that the specific weight of fat people is lower than that of normal persons.

Many of the patients with pituitary or cerebral obesity show marked signs of increased cerebral pressure: headache, slow pulse rate, tendency to vomit, nausea, subfebrile temperatures, tendency to retain water and salt, and a high metabolic rate in the morning. If one does a spinal puncture the spinal pressure is found increased. One is forced mostly to let ooze out about 40 to 60 cc. until the pressure becomes normal. This procedure lowers the cerebral pressure for some time; in rare cases we get even a lasting effect. Most of the complaints disappear shortly after the puncture. It is very interesting that the puncture produces marked change in many regards. The basal metabolism rate shows a notable decrease, the temperature comes to normal and the disturbances as to the water metabolism are no longer found. These three phenomena are not combined physiologically. We find the change of the metabolic rate also in patients who do not show any change as to the temperature as there was no rise in temperature at all.

The high metabolic rate of these patients with cerebral obesity offers many other interesting features. It is possible to lower it by average or high doses of preparations of the anterior lobe of the pituitary gland, or by very small doses of thyroid preparations. It is interesting that as a rule the respiratory quotient also comes down to a normal rate by these modifications.

Surveying the whole literature of obesity, especially since 1900, and adding the new investigations of my own, one must come to the conclusion that the ideas we have had until now upon the pathogenesis of obesity are not apt to explain all the different facts involved. It is impossible to consider a certain endocrine gland as the cause of obesity. Many of them may be of importance. However, never the endocrine gland alone gives the decision, for we see the same disturbances of the gland without an obesity resulting. Hypothyroidism is found very often without obesity and so are hypogenitalism and hyperpancreatism, and so on.

The regulation of the weight of man is quite the same as the regulation of temperature. The most important factor is the function of the regulative center in the central nervous system. This center is located at the base of the brain in the hypothalamus somewhat behind the tuber cinereum. This region is very near to the pituitary body and it is diffi-

cult to explain the role of this gland. As things are up to date I think it is best not to try to separate the role of the hypophysis from that of the hypothalamic centers. About eight years ago Biedl, one of the best known endocrinologists of the world, pointed out that the hypophysis functionally forms a physiological unity with these centers and I think that even now we cannot give a better explanation. Nevertheless, the analysis must be studied further. On the other hand, I am of the opinion that as to the clinical standpoint it does not make much difference whether we apply a treatment to the pituitary body itself or to the region near by.

The regulation of the body weight is a very complex problem. Many lesions and changes in the different organs are apt to bring out a tendency for gaining weight, but the weight will change only if the central regulation fails. The clinic shows this every day. If you extirpate the ovaries of ten women not all ten will develop obesity, only four or five. Very often the central regulation succeeds in keeping the old weight even under such a disturbance of the endocrine balance suddenly applied. The small appetite of the myxedematous patients is one of these regulative signs to keep the weight.

But in case the central regulation fails the weight will change. This failing can occur in a quite healthy central regulation, when the demands given to it by the different changes are too strong. Very often the central regulation itself is not all right, maybe there is a weakness of primary origin or that secondary disturbances occur. It is very interesting that during the last twenty years from all countries of the world such cases of central nervous disturbances leading to severe obesity have been published: I mean the obesity after encephalitis, the so-called post-encephalitic obesity. Here we deal with very clear conditions as histological demonstration is possible. The same effect of circumscript lesion of the central nervous system is given in cases of tumor of the brain and of softening of the brain occurring in arteriosclerotic processes.

From the standpoint of the views and ideas given here the whole problem of body weight can be explained, overweight and underweight being included. Also partial obesity can be discussed in this line, the big nervous factor in these cases has been stated very often. I wish to mention only two points as to partial obesity. I think there is enough proof to state that the different endocrine glands do not influence the subcutaneous tissues of the whole body in the same measure. The thyroid, for instance, is more active in the upper parts of the body, whereas the region of the girdle, hips and the lower extremities yield more to the endocrine secretion of the gonads. Many women after castration or after the menopause show marked increase of fat at the hips but decrease of fat in the upper parts of the body. In Basedow's disease we are accustomed to see meagerness, especially in the upper part of the body. I think that this phenomenon is a remnant of the original metameric structure of our body.

The problem of partial obesity has also to deal with the theories of primary lipogenic tendency of the peripheral tissues. These theories were

started by F. Kraus and G. v. Bergmann in Germany. But even if one agrees with these theories the central regulation will play its role. Only in case that this center fails to bring forth the reactions necessary to avoid such a local process, partial obesity will be possible.

The view of the predominant factor of the central regulation as regards the body weight is well supported by a series of experimental findings. I only mention the names of the authors as it is impossible to go into details: Aschner, Bailey and Bremer, P. E. Smith, Foster, Benninghoven, Raab, Grafe, and Grünthal.

The standpoint brought out is of high importance for the clinical work. Three points may be discussed:

(1) It is no more possible to base the total daily metabolic rate of obese people on the amount of the so-called basal metabolism by adding certain amounts as to the reaction of intake of food and of the muscular work carried out during the day. The role of the "negative phases" must be considered; it is possible that these negative phases balance the positive phases during the day.

(2) When we assemble the different symptoms and findings presented by an obese patient, we must not try to consider them all as simple signs of the disease. Some of them may be the expression of reactions of the body to the obesity developed. One of these symptoms, that surely plays the role of a reaction, is the normal or high metabolic rate that many obese show in the morning.

(3) It is very important to look for symptoms that indicate a disturbance of the central regulation: signs of increased cerebral pressure, lethargy, or nervous symptoms. A very accurate history must be taken as to these symptoms.

(4) It is necessary to give a new classification of the different kinds of obesity. The division into exogenous and endogenous obesity now prevailing must be discontinued. Most of the cases are mixed as to this regard. I include in my scheme also the pure exogenous cases. It is true that these people are not really sick and do not offer any organic disturbances, but the physiological problem is the same. The normal organism and the normal central regulation can stand only a certain amount of overeating. The limit is very different for individual people. It is one of the most important factors of the so-called constitution or condition of the body. The most important factors may be shortly mentioned:

(a) The resistance of the body against changes of the pH.

(b) The resistance of the body against changes in weight.

(c) The resistance of the body against changes in temperature.

(d) The resistance of the body against infection.

In all these fundamental things the nervous system is highly involved and I think that under the view of phylogenesis these functions are the

foremost and oldest of the nervous system. The location of the different centers concerned reveals the same as they are all situated in the phylogenetically oldest parts of the central nervous system.

The following is the classification of obesity that results from my investigations:

I. Obesity as the result of primary disturbances of the central regulation of metabolism.

A. Purely cerebral disturbance (encephalitis, tumor, etc.)

B. Purely pituitary disturbance.

C. Mixed forms.

II. Obesity as the result of secondary functional disturbance of the central regulation of metabolism, as primary disturbances may act:

A. Endogenous factors:

(1) Disturbances of general behavior (such as of hunger, thirst, and activity).

(2) Disturbances of the endocrine glands:

(a) Single glands: thyroid, gonads, adrenals (especially cortex), pancreas, pineal.

(b) Pluriglandular disturbances.

(3) Disturbances of the periphery (primary lipogenic tendency of the tissues according to theories of Fr. Kraus, and G. v. Bergmann).

B. Exogenous factors:

(1) Overeating.

(2) Muscular inactivity.

(3) Mixed forms.

As to the therapy of obesity I wish to mention the following points:

(1) It is best to take the metabolic rate in every case of obesity. If we deal with an adult person and no complications are present, especially no disease of the circulatory system and of the kidneys, and of the liver, it is indicated to give a diet that is equal only to the amount of the metabolic rate in the morning (standard metabolism). The patients may have slight muscular exercise every day. As to the diet, 0.8 to 1.0 gm. of proteins for every kilogram of the calculated normal weight of the patient is sufficient to avoid disturbances of the nitrogen metabolism. Even under a very strict diet this amount must never be decreased markedly. The rest of the calories are divided among carbohydrates and fat in such proportion that the ketogenic-antiketogenic ratio is about 1.5 to 1, but should not exceed this amount. This would be the highest ratio of fatty acids and

glucose without ketonuria as was shown by R. T. Woodyatt and others. Woodyatt's formula is in this case:

Fat (in gm.) = 2 × Carbohydrates (in gm.) + ½ × Proteins (in gm.). Hence, a diet of

50 gm. of proteins.
40 gm. of carbohydrates.
105 gm. of fat.

would show the ketogenic-antiketogenic ratio of 1.5 to 1. Also the formulae of P. A. Shaffer, of R. S. Hubbard and F. R. Wright and of R. M. Wilder and M. D. Winter may be used. Very often it is advisable to begin with a diet that shows a ketogenic-antiketogenic ratio of 1.0 to 1.0.

If it appears necessary to restrict the diet even more and to go below the number of calories equal to the standard metabolic rate of the patient, it should be done by reducing the amount of the fat, keeping proteins and carbohydrates on the previous level. However, this whole dietary procedure does not apply to every case as sometimes individual factors interfere with its routine application. It is advisable to keep the patients under strict observation long enough to make sure that they agree with the diet. Vitamines and Calcium must be considered in the diet. Fluid intake must not exceed 800 to 1000 cc. a day; salt not over 7 to 8 gm. per day. It is striking what effects are obtained by such a dietary procedure. Similar good results were reported recently by F. A. Evans and J. Strang (Pittsburgh).

(2) Light muscular work, as a rule, does not cause any noticeable effect as to loss of weight. On the contrary, rest therapy sometimes produces better results. Heavy work naturally is effective, but it is mostly not without danger as to secondary disturbances, especially of the circulatory system.

(3) If it is not possible to give such a strict diet, good preparation of the anterior lobe of the pituitary gland is advisable. Rather high doses must be given. I obtained very good results with the German preparation, "Praephyson," in doses of 3 to 8 tablets a day or 1 cc. subcutaneously. It is indicated to add very small amounts of thyroid preparations, a half to one tablet a day or every second day. High doses of thyroid are very dangerous and must never be used. Ovarian preparations are mostly without any effect on obesity.

(4) A cautious protein therapy may be tried and is often a good adjuvant.

(5) Careful roentgen treatment and diathermy of the pituitary body and the adjacent parts of the brain have been started in many clinics. They seem to be of value in some cases, but it is impossible to draw definite conclusions from the small number of observations.

(6) The loss of weight must never be too fast in order to avoid secondary disturbances.

The principal point of this paper is to give a new aspect to the problem of obesity as a problem of caloric balance. There is no proof until now that the laws of caloric balance do not hold in obesity. In this regard my work is in line with the investigations that Newburgh and his associates published recently.

As to the technic of my investigations I wish to add some remarks about the basal metabolic rate, *"standard metabolism."* Nearly all investigators agree that it is necessary to take the metabolic rate not before twelve to fifteen hours after the last intake of food. As to the muscular work there occur many differences in the technic. In many institutes complete rest of from twenty to thirty minutes is considered sufficient for taking the basal metabolic rate, others require a rest of one hour or more. My investigations show that the influence of muscular work on the metabolic rate can be very marked for a long time. It is important to state that the metabolic rate determined shortly following muscular work may be either higher or lower than the real metabolic rate in the morning at complete rest. If one wishes to get absolutely exact and constant amounts for the basal metabolic rate it is not only necessary to take the rate twelve to fifteen hours after the last intake of food, but also to observe complete rest during these hours. These conditions can only be fulfilled under hospital treatment, where the patients are brought to the apparatus in their beds or the apparatus transferred to them. If there was only slight muscular work carried out, for instance, a walk of not more than half a mile, a rest of three to four hours would be sufficient to free the body of the influence of the muscular work.

The big difficulties involved in the technic and theory of the basal metabolism have been pointed out by Benedict (1915). Everyone dealing with these things should read it. In this paper Benedict showed that there are conditions under which the metabolic rate sinks during sleep at night markedly below the level of the so-called basal metabolism taken in the morning at complete rest. This is one of the best examples of negative phases. And to be sure the negative phases during sleep play a role in certain cases of endogenous obesity and are an important factor in my criticism of the basal metabolism as a basis for the calculation of the total twenty-four hour metabolism. These facts with others lead to the conviction that the "basal metabolism" is not at all the "minimum metabolism" of a person as many authors maintain. Besides this, many investigations have shown that the amount of the so-called basal metabolism may be markedly altered very often by factors that obviously have no, or nearly no, influence on the amount of the total metabolic rate of 24 hours (Benedict, Arnoldi, my own investigations). In practical daily routine work it is completely impossible to eliminate all these factors.

To better illustrate my contentions some curves are offered that show the negative phases occurring in obese people after slight muscular exercise consisting of flexing each leg eight times a minute, while lying down. Figure 1 gives the curves of two patients:

Patient N. (thirty-nine years of age, 176 cm. tall, and 102.0 kgm. in weight), who showed a typical case of overeating; his weight could be easily reduced by slight dieting. It is interesting to see that he did not offer any negative phase after muscular work. The other subject, Patient

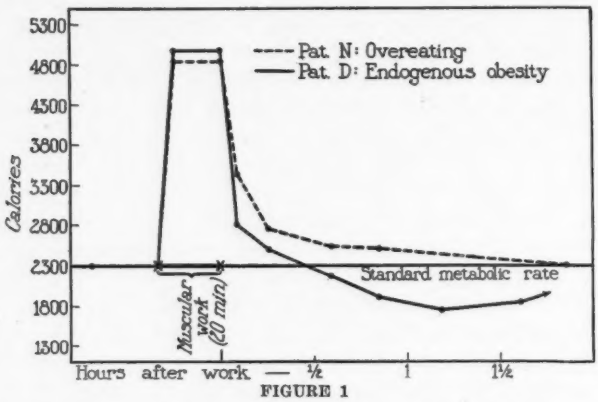


FIGURE 1

D. (forty-nine years of age, 168 cm. tall, and 103.0 kgm. in weight), showed a typical case of endogenous, so-called cerebral obesity. It was very difficult to influence his weight as it yielded only to a very strict diet. The basal metabolic rate of the two patients was almost identical, a fact that permits good comparison. Patient D. showed a rather marked negative phase after muscular work.

Figure 2 gives an idea of the extent that negative phases may reach in the patients with endogenous obesity, especially in cases with a high

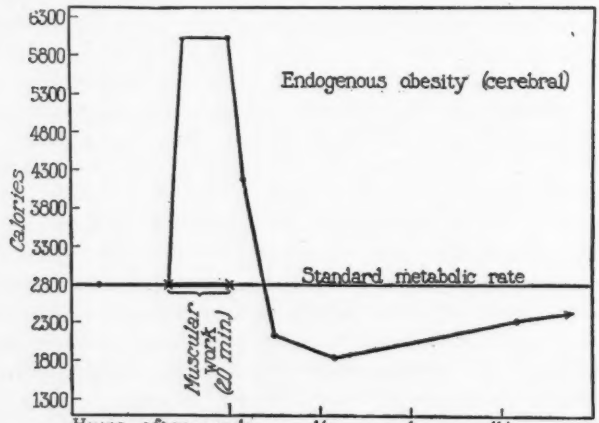


FIGURE 2

metabolic rate in the morning ("standard metabolism"). This is a curve of Patient Pr. (fifty-one years of age, 187 cm. tall, and 138.5 kgm. in

weight), who showed a typical endogenous obesity of cerebral character. His standard metabolism was carefully observed and always proved to be rather high (2848.5 calories).

In both figures the standard metabolic rate (basal metabolism) is taken as the horizontal axis, so that the positive phases are above the axis, the negative phases below. The areas bounded by the axis and by the curve give an exact picture of the caloric amounts on the positive and negative sides so that a simple geometrical comparation gives the balance. All the metabolic amounts are calculated for twenty-four hours and therefore direct comparation is possible.

Whoever is interested in the problems brought out here may read my compiled paper on the subject (Bernhardt, 1929). A review of the literature is also given.

SUMMARY

(1) The method of calculating the total daily metabolic amount in a person by adding three factors, (a) basal metabolic rate (standard metabolism), (b) caloric amount necessary for the muscular exercise during twenty-four hours, and (c) caloric amount due to the reaction to the intake of food (specific dynamic action of food), was introduced by von Noorden and Magnus-Levy, about thirty years ago. It was believed to be applicable to obese as well as normal people. The studies pointed out in this paper prove that this method does not hold in many cases of obesity, especially that of endogenous obesity.

(2) It was shown that many obese people do not lose weight on a diet calorically equal to their own basal metabolic rate as ordinarily determined, even when given for many weeks. Water and salt metabolism was always carefully taken account of in all of these experiments.

(3) It was demonstrated that there are periods during the day when the metabolic rate sinks markedly under that determined in the morning. These periods of decreased metabolism are found especially during the time of gaining weight. They are evident more after light muscular work than after the intake of food and they occur very often during sleep. I call these periods "negative phases." They can be found in such a degree that they form a complete balance against the positive phases occurring during twenty-four hours so that the whole metabolism rate of the day may show about the same amount as the so-called basal metabolic rate of these patients. The negative phases are seldom found during the time of loss of weight.

(4) It is very interesting to state that negative phases may also occur in normal people under certain conditions. Convalescents from severe diseases during the state of rapid gain in weight are the best examples.

(5) These investigations may give an explanation for the cases described in literature in which obese people did not lose under a very strict diet (Grafe, A. Loewy, Hausleiter, S. Strouse, von Noorden, and others).

(6) As to the etiology of obesity, my experiences lead to a standpoint different from that generally accepted. It is impossible to accuse a particular endocrine gland of being the cause of obesity; disturbances of the endocrine glands are often involved but they do not play the first role. The decisive factor is the function of the hypothalamic regulative center. The regulation of weight closely resembles the regulation of body temperature. The center can be disturbed directly, as for instance in encephalitis or tumor of the brain, or it can fail when the demands directed on it by peripheral disturbances (disturbances of endocrine glands, changes in the peripheral tissues, changes in general behavior, such as hunger, thirst, et cetera), are too great. These new conceptions involve the whole problem of weight, both overweight and underweight.

(7) My experience also leads to the conviction that we must change our opinion about the metabolic rate taken in the morning at complete rest at sufficient time after the last muscular work and twelve to fifteen hours after the last intake of food. The term "basal metabolism" is no more advisable. It would be better to use the term "standard metabolism" (A. Krogh and E. F. Du Bois). The problems of the so-called "basal metabolism" are very complex and are partly discussed in this paper.

BIBLIOGRAPHY

1. Arnoldi, W.: Ztschr. f. klin. Med. **92**: 187. 1921. **94**: 268. 1922.
2. Arnoldi, W. and E. Leschke: Ztschr. f. klin. Med. **92**: 364. 1921.
3. Aschner, B.: Berl. klin. Wchnschr. **53**: 772. 1916.
4. Bailey, P. and F. Bremer: This Journal, **5**: 761. 1921.
5. Benedict, F. G.: J. Biol. Chem. **20**: 263. 1915.
6. Benedict, F. G. and E. P. Cathcart: Carnegie Inst. Washington No. 187. 1913.
7. Benedict, F. G. and F. B. Talbot: Carnegie Inst. Washington No. 320. 1921.
8. v. Bergmann, G.: Deutsche med. Wchnschr. **35**: 611. 1909.
   Ztschr. f. exper. Path. u. Therap. **5**: 646. 1909. **10**: 339. 1912.
   Im Handbuch der Biochemie (Oppenheimer) 2. Aufl. **7**: 562. 1927.
9. Bernhardt, H.: Ztschr. f. klin. Med. **99**: 149. 1924. **107**: 488. 1928.
   Klin. Wchnschr. **6**: 1493. **7**: 602. 1928. **9**: 65, 399. 1930.
   Erg. Inn. Med. u. Kdhlk. **36**: 1. 1929.
10. Bernhardt, H. and H. Schlesener: Ztschr. f. klin. Med. **107**: 133. 1928.
11. Biedl, A.: Verh. Inn. Kongr. Wiesbaden **34**: 331. 1922.
    Innere Sekretion, 3. Aufl. 1916.
12. Dercum, F.: Adiposis dolorosa, Univ. med. Magaz. 1888.
13. Du Bois, D. and E. F. Du Bois: Arch. Int. Med. **17**: 863. 1916.
14. Düring, M.: Cor.-Bl. f. schweiz. Aerzte, **44**: 1425. 1914.
15. Dürr, R.: Klin. Wchnschr. **4**: 1496. 1925.
16. Eidelsberger, J.: Ann. Int. Med. **3**: 604. 1929.
17. Evans, F. A. and J. M. Strang: Am. J. M. Sc. **177**: 339. 1929.
18. Foster, G. L. and C. D. Benninghoven: J. Biol. Chem. **70**: 285. 1926.
19. Foster, G. L. and P. E. Smith: J. A. M. A. **87**: 2151. 1926.
20. Froelich, A.: Wien. klin. Rdsch. 1901. Wien. klin. Wchnschr. **15**: 27. 1902.
21. Gessler, H.: Deutsches. Arch. f. klin. Med. **157**: 36. 1927.
22. Grafe, E.: Deutsches. Arch. f. klin. Med. **102**: 15. 1911. **113**: 1. 1914. **133**: 41. 1920.
23. Grafe, E. and D. Graham: Ztschr. f. physiol. Chem. **73**: 1. 1911.
24. Grafe, E. and E. Grünthal: Klin. Wchnschr. **8**: 1013. 1929.
25. Grafe, E. and R. Koch: Deutsches. Arch. f. klin. Med. **106**: 564. 1912.
26. Harris, I. A. and F. G. Benedict: Carnegie Inst. Washington, No. 279. 1919.
27. Hausleiter, H.: Ztschr. f. exper. Path. u. Therap. **17**: 413. 1915.
28. Hubbard, R. S. and F. R. Wright: J. Biol. Chem. **50**: 361. 1922.
29. Jaquet, A. and N. Svenson: Ztschr. klin. Med. **41**: 375. 1900.
30. Karell, T.: Arch. gen. de med. **2**: 513; 694. 1866.
31. Kestner, Plant and Schadow: Klin. Wchnschr. **5**: 1646. 1926.
32. Knipping, H. W.: Klin. Wchnschr. **4**: 2047. 1925.
33. Kraus, Fr.: Lehrbuch von Mehring-Krehl, 2. Aufl. **2**: 164. 1925.

34. Lauter, S.: Deutsches. Arch. f. klin. Med. **150**: 315. 1926.
35. Leschke, E.: Med. Klin. **22**: 1563. 1926.
36. Leven, G.: Press méd. **33**: 1651. 1925.
37. Liebesny, P.: Klin. Wchnschr. **4**: 156. 1925.
38. Loewy, A. and F. Hirschfeld: Deutsche med. Wchnschr. **36**: 1794. 1910.
39. Lortat-Jacob, L. and G. Vitry: Rev. de méd., Paris, **29**: 184. 1909.
40. Lublin, A.: Klin. Wchnschr. **8**: 2276. 1929.
41. McCaskey, D.: Am. Med. **22**: 17. 1927.
42. Magnus-Levy, A.: Ztschr. f. klin. Med. **33**: 269. 1897. Id. **52**: 201. 1904. Id. **60**: 177. 1906. In v. Noorden's Handbuch der Stoffwechselpathologie, 1907.
43. Mansfeld, G. and F. Müller: Arch. f. d. ges. Physiol. **152**: 61. 1913.
44. Means, J. H.: Arch. Int. Med. **17**: 704. 1916. J. Med. Research, **32**: 121. 1915.
45. Minnig, A.: M. J. and Rec. **126**: 171. 1927.
46. v. Müller, F.: Deutsches Archiv f. klin. Med. **51**: 335. 1893. Ztschr. f. klin. Med. **16**: 496. 1889.
47. Neumann, R. O.: Arch. f. Hyg. **45**: 1. 1902.
48. Newburgh, L. H. and M. W. Johnston: J. Clin. Invest. **8**: 197. 1930. and Ann. Int. Med. **3**: 815. 1930.
49. v. Noorden, Carl: Die Fettsucht, 2. Aufl. Leipzig, 1910, und Med. Klinik **5**: 1. 1909.
50. Plaut, R.: Deutsches. Arch. f. klin. Med. **139**: 285. 1922.
51. Raab, W.: Wien. Arch. f. klin. Med. **7**: 443. 1924. Ztschr. f. d. exper. Med. **49**: 179. 1926. **53**: 317. 1927. **62**: 366. 1928.
52. Rabe, F. and R. Plaut: Deutsches. Arch. f. klin. Med. **137**: 187. 1921.
53. Rolly, Fr.: Deutsche med. Wchnschr. **47**: 887. 1921.
54. Rubner, M.: Gesetze des Energieverbrauches u. der Ernährung, Berlin, 1902. Beiträge zur Ernährung im Knabenalter mit besonderer Berücksichtigung der Fettsucht, Berlin, 1902.
55. Salomon, H.: Ueber Durstkuren. v. Noorden's klinische Abhandlungen Bd. **6**: 1905.
56. Schwenkenbecher, A.: Deutsches. Arch. f. klin. Med. **79**: 29. 1904.
57. Shaffer, P. A.: J. Biol. Chem. **47**: 449. 1921.
58. Smith, P. E.: Am. J. Physiol. **81**: 20. 1927. J. A. M. A. **88**: 158. 1927.
59. Smith, P. E. and J. P. Graeser: Anat. Rec. **27**: 219. 1924.
60. Smith, P. E. and C. F. Greenwood: Anat. Rec. **29**: 373. 1925.
61. Staehlin, R.: Deutsche med. Wchnschr, **35**: 609. 1909.
62. Strouse, S., C. C. Wang and M. Dye: Arch. Int. Med. **34**: 267; 275. 1924. **36**: 397. 1925.
63. Talbot, F. B.: Am. J. Dis. Childr. **20**: 331. 1920.
64. Umber, F.: Med. Klinik **9**: 2014. 1913.
65. Wang, C. C., S. Strouse and Z. O. Morton: Arch. Int. Med. **45**: 727. 1930.
66. Wilder, R. M. and M. D. Winter: J. Biol. Chem. **52**: 392. 1922.
67. Woodyatt, R. T.: Arch. Int. Med. **28**: 125. 1921.
68. Zondek, H.: Deutsche med. Wchnschr. **49**: 339. 1923. **51**: 1267. 1925. Med. Klinik **24**: 685. 1928.
69. Zondek, H. and H. Bernhardt: Klin. Wchnschr. **4**: 1488. 1925.

THE EFFECT OF INSULIN UPON THE RATE OF DIALYSIS OF DIABETIC BLOOD SUGAR*

ISRAEL S. KLEINER

With the Assistance of

HAROLD BIRNKRANT
AND
THEODORE ROTHMAN

From the Department of Physiological Chemistry of the New York Homeopathic Medical College and Flower Hospital.
NEW YORK
and
The Biological Laboratory
COLD SPRING HARBOR, L. I.

In 1918 one of us (1) compared the rate of dialysis of the blood sugar of diabetic dogs' blood with that of glucose, which had been added to the blood of normal animals. The diabetic blood sugar dialyzed at an irregular rate. The curve usually indicated a delay or even a complete cessation of dialysis during one or more periods, whereas the control dialysis proceeded in a regular, uninterrupted manner.

Although various explanations were offered, the one which appeared most tenable was that part of the blood sugar in diabetes is present in combined form and part free. If the former dialyzed slowly and the latter rapidly and if the combined sugar, after most of the free sugar had dialyzed out, was convertible into free glucose, curves of the type obtained would be possible. We have been engaging in various investigations in the attempt to throw more light upon this phenomenon. One of the first questions which arose was whether insulin would affect this peculiar diabetic dialysis curve. The present note deals with that question.

Since our findings are uniform we need only give two typical experiments, although we have other similar results. One of these is of special interest because it was one of a series in which we used a certain diabetic animal (Dog No. 3), which for a long time apparently gave "normal" curves. This fact was quite perplexing and delayed our investigations until it was finally discovered that, in this particular animal, the period of inhibited dialysis usually occurred quite late, instead of during the first two hours. We have no explanation for this unusual result.

Methods. The same general methods, described in the earlier paper were employed. Twenty to fifty cubic centimeters of hirudinized blood were divided in two portions, and each was placed in an animal parchment dialysis bag. Dry insulin[1] (from 1 to about 150 units) was added to one

*Aided by a grant from the Elizabeth Thompson Science Fund.

[1]We are indebted to Eli Lilly and Company for this preparation. It was labelled "approximately 20 units per milligram," but, as it had been prepared about two years before it was sent to us, it had deteriorated slightly. It was, however, exceedingly potent.

portion; it was then mixed thoroughly to insure solution of the insulin. The other portion had no insulin added. Each was now immersed in 500 cc. or 1000 cc. of Ringer's solution containing glucose (usually 0.15%). In some of the first experiments with the blood of Dog No. 3, novirudin and medicinal insulin solution (Lilly) (from 8 to 12 units) were employed instead of hirudin and dry insulin, respectively. Samples were taken before dialysis, and at intervals during its course. At each sampling, the dialysis bag was removed from the bath to permit of proper mixing and sampling of the blood. Sugar was determined by Myers and Bailey's modification of the Lewis-Benedict method.

Results.[2] Curves I and II in Figure 1 show the results of one of the experiments upon the animal mentioned above. Both dialyses proceeded regularly until the sixth hour, at which time, dialysis apparently

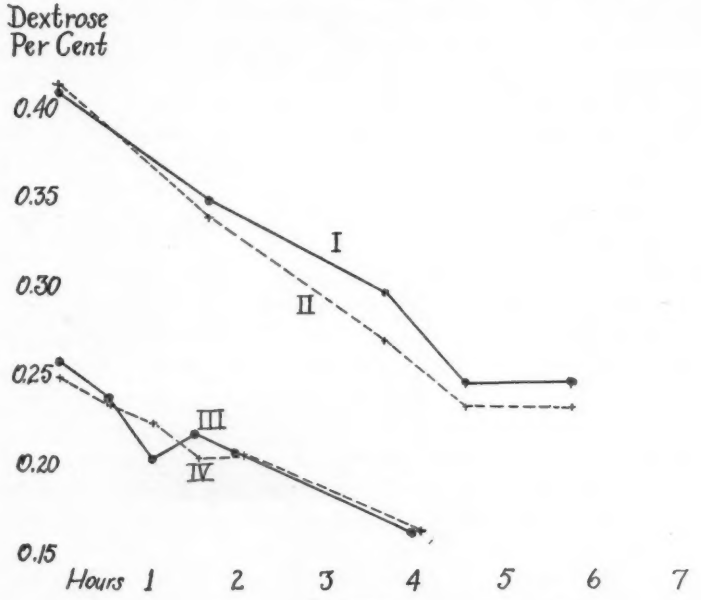


FIGURE 1.

I and II represent two dialyses of diabetic dog blood (from Dog 3) carried on simultaneously; I (solid line) had 1 mg. dry insulin added to 10 cc. of blood; II (broken line) contained no insulin. III and IV similarly represent simultaneous dialyses of two portions of diabetic dog blood (from Dog 4); III (solid line) contained 5.8 mg. of dry insulin in 22 cc. of blood; IV (broken line) contained no insulin. All four dialyzed against 0.15 per cent dextrose in Ringer's solution.

stopped in both cases, although the percentage of sugar was still well above that in the fluid against which it was dialyzing. The insulin added to I did not change the rate of dialysis, when compared with II. Curves III and IV, representing an experiment with blood from another diabetic

[2] A preliminary reference to this work was included in the report of Kleiner, I. S., and Bell, M., Am. J. Physiol. 90: 410 (1929), presented before the XIIIth International Physiological Congress, August 22, 1929.

animal, while not coinciding so closely, manifest the same general trend. Either could be considered a typical diabetic curve. Curve III (with insulin) not only is not more "normal" than IV, but even has a greater period of delay. There were very few experiments in which such simultaneous curves duplicated each other as closely as Curves I and II. This is not strange when it is remembered that the membranes used were of animal parchment, no two of which can be absolute duplicates. However in no case did insulin tend to increase the general rate of dialysis of the blood sugar or make the curve more uniform than that of the control, which had no insulin. This is true also for a single experiment in which human diabetic blood was employed.

It is thus evident that insulin does not produce its effect by any action which tends to make the blood sugar more diffusible. That is, if this phenomenon is due to the presence of glucose in combined form in diabetic blood, insulin does not break the combination.

The extensive literature on insulin affords no clear-cut evidence of any definite effect of insulin upon blood sugar *in vitro*. There is no agreement regarding its effect upon glucolysis; quite as many investigators find that it hastens glucolysis (2) as the reverse (3). Although our experiments can not fairly be considered true tests of glucolysis, still if insulin has a marked effect upon this phenomenon, it would be expected to influence these curves. Pico and Negrete (4) have stated that insulin increases the permeability of collodion sacs, Cuenca (5) reports that it permits of more rapid penetration of sugar into muscle, and Rona and Sperling (6) and Loewi (7) found that red blood cells take up sugar more easily under the influence of insulin. No similar increase in the permeability of the parchment membrane used by us was observed.

SUMMARY

Dry potent insulin, added to diabetic blood (dog's), has no effect upon the rate of dialysis of the blood sugar, nor does it have any apparent influence upon the permeability of animal parchment membranes.

BIBLIOGRAPHY

1. Kleiner, I. S.: J. Biol. Chem. **34**: 471. 1918.
2. Bierry, H., F. Rathery and Kourilsky: Compt. rend. Soc. de Biol. **90**: 417. 1924
Bierry, H. and L. Moquet: Compt. rend. Soc. de biol. **93**: 322. 1925.
Kauffmann-Cosla, O. and J. Roche: Bull. Soc. chim. biol. **8**: 636. 1926.
Homma, Jun: Jap. J. M. Sc. Tr. (Sect. II), **1**: 165. 1927.
3. Eadie, G. S., J. J. R. Macleod and E. C. Noble: Am. J. Physiol. **65**: 462. 1923.
Nitzescu, I. I. and C. Popescu-Inotesti: Compt. rend. Soc. de biol. **90**: 534. 1924.
Ducceschi, V.: Boll. soc. med. chir. di Pavia, 35: 215. 1924. Through Chem. Absts. **19**: 1900. 1925.
Kawashima, Y.: J. Biochem. **4**: 429. 1925.
4. Pico, C. E. and J. Negrete: Compt. rend. Soc. de biol. **92**: 905. 1925.
5. Cuenca, B. S.: Biochem. Ztschr. **190**: 1. 1927.
6. Rona, P. and M. Sperling: Biochem. Ztschr. **175**: 253. 1926.
7. Loewi, O.: Naturwissenschaften, **15**: 93. 1927.

CORTIN, VITAL HORMONE OF THE ADRENAL CORTEX*

FRANK A. HARTMAN
University of Buffalo
BUFFALO

The cortex of the adrenal gland produces a hormone which is essential to life. Without it appetite fails, weight is lost and marked muscular weakness develops ultimately leading to prostration and death.

We have already described a method by which a dilute solution of this hormone can be prepared (1). The method is limited because the sodium chloride content determines the degree of concentration. An acidulated extract is saturated with NaCL. The hormone is carried down with the resulting precipitate. Ethyl alcohol (80 per cent) dissolves the hormone but coagulates the protein in this precipitate. The alcohol is removed by distillation *in vacuo*. Water is added to the residue to make the NaCL isotonic with the body fluids. Recognizing the limitation which the employment of NaCL put upon our product, we have been working on the use of solvents and are finally ready to report a satisfactory process.

PREPARATION OF A CONCENTRATED EXTRACT

Any desired concentration of the hormone can be prepared by the following method: Cortical material is extracted with ether. After removal of the ether by distillation *in vacuo* the ether residue is extracted with warm 80 per cent alcohol which dissolves the hormone. Fatty substances are filtered off. Alcohol is removed *in vacuo* and the residue taken up with water to make any desired concentration. An extract almost free from epinephrin can be made by extracting the alcoholic residue with a small volume of ether.

Swingle and Pfiffner have also prepared a concentrated extract of the adrenal cortex (2).

We have previously suggested *cortin* as the name for the adrenal cortical hormone essential to life. For convenience we so designate it in this communication.

CORTIN AS A SUBSTITUTE FOR THE ADRENAL GLAND

Cats with both adrenals removed have been furnished with cortin by subcutaneous injection. Eight cats have been so treated. The adrenals were removed in two operations in six and at one operation in two animals.

Cats whose adrenals have been removed in two operations survive indefinitely if treated with sufficient cortin. Of the series treated with

*Read before the Fourteenth Annual Meeting of the Association for the Study of Internal Secretions, Detroit, Michigan, June 23, 1930.

concentrated extract five are alive at the present time. The second adrenal was removed 39, 54, 61, 74, and 170 days ago, respectively. The sixth animal died at 41 days because the extract was discontinued, the intention being to let the animal pass into the last stages of insufficiency, then attempt to revive him. When the time came to revive him the extract used proved later to be both toxic and of no potency and therefore failed.

Of the two animals whose adrenals were removed at a single operation (by the lumbar path) one is alive at 28 days. The other cat lived 6 days but never recovered sufficiently to eat. She was a young cat that had had kittens a short time before.

All live cats are doing well, living a perfectly normal existence as long as we inject cortin in sufficient amounts twice daily. They eat as well as, or better than, normal. We know this to be true by comparison

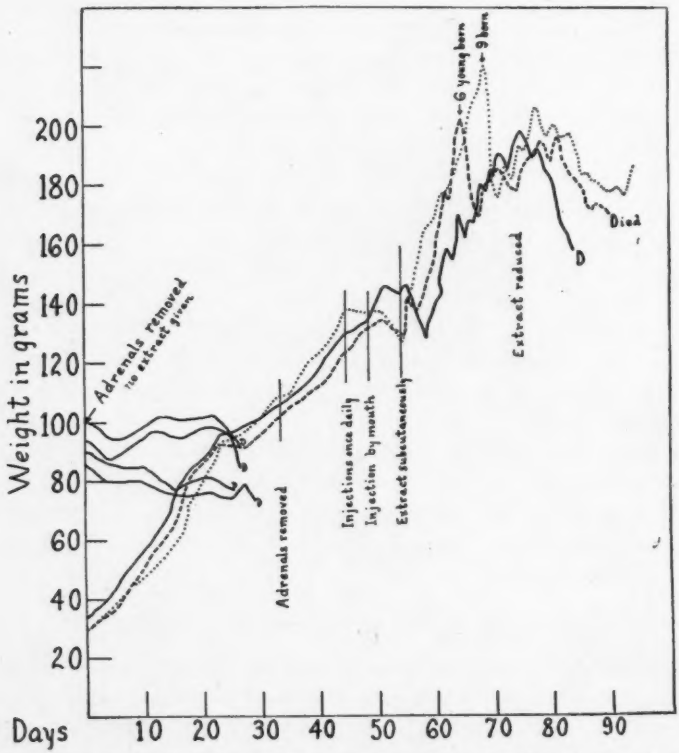


Fig. 1. Growth of rats before and after removal of both adrenals. Removal of adrenals at time indicated by arrow. Cortin injected twice daily.

with normal cats and in three of the animals we have daily records of the food consumption over a period of four months preceding the removal of the adrenals.

They gain in weight. Sometimes slowly, sometimes rapidly. This probably depends upon the individual and upon the amount of cortin administered. As an illustration, Cat RV weighed 2610 grams at the time of the second adrenal removal. At fifty-one days she weighed 2920 grams, a gain of more than eleven per cent.

In connection with the gain in weight, it is significant to point out that growing rats continue to grow unabated after both adrenals are removed if cortin is injected. Four rats of the same litter were injected twice daily with cortin after the removal of both adrenals. They continued to grow as fast as before the operation (Fig. 1). They also showed the activity of normal young rats.

Blood urea. Blood urea has been studied from time to time in all cats treated. When it becomes high, the injection of cortin lowers it. If low there is no effect (Table I).

TABLE I

BLOOD UREAS IN CORTIN TREATED ADRENALECTOMIZED CATS

Cat	Days After Operation	Time of Day		Blood Urea mgm. per 100 cc.
OZ	15	9:00 a.m.	Cortin injected.....	68.4
		12:00 m.	.....	54.0
	18	9:00 a.m.	Cortin injected.....	84.9
		12:00 m.	.....	62.9
ON	Before	9:00 a.m.	.....	39.0
		12:00 m.	.....	45.0
	21	10:00 a.m.	.....	52.6
		1:00 p.m.	.....	57.2
	23	9:30 a.m.	Cortin injected.....	55.4
		12:30 p.m.	.....	57.7
RV	48	10:00 a.m.	.....	93.8
		12:30 p.m.	.....	92.3
	52	9:30 a.m.	Cortin injected.....	80.0
		12:24 p.m.	.....	58.0

Behavior. Adrenalectomized cats treated with adequate amounts of cortin behave like normal cats. They run, fight and play. One cat has been in heat. They show the usual interest in their surroundings, being alert and quick to respond to various stimuli. If cortin is reduced appetite fails, and asthenia develops.

Resistance to infections and recovery from operations. Untreated adrenalectomized cats show a low resistance to infections, often dying of respiratory infection. If they are operated upon recovery is unlikely or for a short time only, the ordeal reducing the survival period. Treated with cortin similar animals possess a high resistance to infection. Thus far we have had no infections of the respiratory tract. Two animals have recovered from extensive subcutaneous infections. One cat has been explored thoroughly for accessory cortical bodies while under the influence of ether. The opening was made at the mid-line and the ether was administered for 36 minutes. The animal recovered promptly and is still in good condition. No accessories were found.

As already indicated it is possible to remove both adrenals from a cat at one operation, the animal surviving indefinitely.

Recovery from acute adrenal insufficiency. We have succeeded in bringing back to normal health two adrenalectomized cats which were permitted to go so far as to become prostrate from lack of cortin.

Cat RM was in poor condition from having had an abortion. On three successive days she was very weak in the morning when first seen, each day being worse than the preceding day. On the third day she became prostrate. Convulsive twitchings and dyspnea were very marked. Cortin was injected intraperitoneally. In an hour the twitchings had ceased and the breathing had returned to normal. In seventy minutes she was sitting up and in one hundred minutes she was eating. By careful treatment she completely recovered and is gaining weight (64th day).

Both adrenals were removed from cat OZ at one operation. Although treated twice daily with cortin the feces became fluid and tinged with blood on the fourth day. Ten days after the operation an area on the skin of six square inches was discovered with a purulent discharge due to an iodine burn. The ordeal of dressing this region was too much. The cat later became prostrated, dyspnea set in and the extremities became cold. After two subcutaneous injections of cortin the cat recovered sufficiently to eat a little meat and drink some broth. However, it required six hours after the first injection to bring this about.

SUMMARY

We have demonstrated that a substance can be obtained from the adrenal cortex, which not only enables completely adrenalectomized animals to survive indefinitely in good health but to grow. This substance will cause recovery of cases of acute adrenal insufficiency. It also lowers the high blood urea of adrenal insufficiency.

BIBLIOGRAPHY

1. Hartman, F. A., K. A. Brownell, W. E. Hartman, G. A. Dean and C. G. MacArthur: Am. J. Physiol. **86**: 353. 1928.
2. Swingle, W. W. and J. J. Pfiffner: Science **71**: 321. 1930.

THE EFFECTS OF GROWTH PROMOTING AND GONAD STIMULATING PRINCIPLES OF THE ANTERIOR LOBE OF THE PITUITARY ON BASAL GASEOUS METABOLISM IN THE RAT*

MILTON O. LEE AND JULES GAGNON
From the Memorial Foundation for Neuro-Endocrine Research
Harvard Medical School
BOSTON

A considerable amount of work, both clinical and experimental, has been published on the effects of the anterior lobe of the pituitary body on the respiratory metabolism. The most of this work previous to 1928 has been cited by Raab (1) in his review on "Hypophysis and Metabolism," and need not be reviewed here.

In general, the greater part of the clinical evidence has indicated that in patients with anterior lobe deficiency there may be a slight decrease in the basal gaseous metabolism. In cases of hyperactivity of the anterior lobe, as in acromegaly, there is often a slightly increased metabolism. Rowe (2) from his wide experience with the use of several functional tests for determining over- or under-activity of the pituitary is in agreement with this majority opinion. Falta (3), on the other hand, has recently reaffirmed his belief that hyperactivity of the anterior lobe has a tendency to decrease the metabolic level. It is certain that clinically there are not seen the marked disturbances in metabolism with pituitary disorders that are characteristic of thyroid disorders. Indeed, Aub (4) and Boothby (5) have both expressed the opinion that there is little evidence that any part of the pituitary acts as a calorigenic agent, and point out the possibility that the apparent metabolic effects of the pituitary may be mediated secondarily through the thyroid.

Experimentally, Benedict and Homans (6) found that hypophysectomy in dogs resulted in a well marked decrease in the oxygen consumption and carbon dioxide production. These results have been corroborated by several later workers who have used this method of approach.

The obvious objection to both the clinical and experimental evidence is that it does not differentiate between the several active substances that are now known to be produced by the pituitary. It seems probable that there are at least two and possibly more hormone principles produced in the anterior lobe alone (Zondek, 7). In extirpation experiments, when all of these functions are destroyed, the effects may be quite different from those caused by the withdrawal of a single principle. In clinical cases, too, the evidence indicates that there is often an involvement of more than one function of the pituitary.

*Read before the Fourteenth Annual Meeting of the Association for the Study of Internal Secretions, Detroit, Michigan, June 23, 1930.

In experiments on feeding anterior lobe preparations and the injection of various extracts, the results have also been difficult of interpretation, because of the fact that the potency, and even the particular principles contained, were not known. With the production of extracts of the anterior lobe with definite and assayable physiological properties, such as found by Evans and his co-workers for growth, and Zondek and Aschheim for sex gland stimulation, it has become possible to determine the metabolic effects more directly.

MATERIAL AND METHODS

Mature white rats, both males and females, were used as the experimental animals. These ranged in age from 4 to 8 months at the beginning of the experiment, and had shown normal growth and development. The animals served largely as their own controls, but other rats from the same colony stock, of the same age and living under the same conditions, were constantly being used in metabolic determinations and thus served as additional controls.

The basal metabolism was determined by the volumetric oxygen consumption method, with a four-unit, closed system apparatus somewhat modified from that designed by Benedict (8). For animal chambers squat pint jars were used, immersed in a water bath kept at such a temperature that the circulating air was constantly about 29.5° C. When respiratory quotients were desired the carbon dioxide was determined by weighing the proper absorption tubes. The rats were fed with bread and milk on the afternoon of the day previous to a metabolic rate determination, then at 4:00 P. M. the starvation period was begun. The rats were kept over night at a room temperature of not less than 80° F.

The next morning the rats were placed in the jars and at least an hour's rest period given. Metabolism determinations were then begun and continued for 4 to 7 hours. The starvation period was thus from 18 to 24 hours. Each determination represented the length of time for the animal to use 368.4 cc. (1 feed-pump stroke) of oxygen reduced to standard conditions. This time varied from 55 to 150 minutes, and hence from 3 to 6 determinations could be made in the course of the day on each of 4 rats. We have found that the first determination made in the day is often the highest and that the last ones of a long series are often high, a fact in agreement with clinical experience. The other determinations made during the day usually show close agreement, and in any case depend rather closely upon the amount of spontaneous activity which the rat shows. Ordinarily when in the lighted chambers at a temperature above the critical, the animals are content to doze lightly the most of the time. There are usually, however, a few periods of restlessness, washing, sniffing or scratching during the day. These movements are not recorded mechanically with our apparatus but each is noted by an observer in constant attendance. We have been able in almost every case to obtain at least one determination in the course of the day in which no, or only a very slight

amount, of movement occurred. For the basal metabolic rate on the particular day, the one, two, three or more such periods in which only the minimal activity occurred were usually averaged together. A critical analysis of the record is essential, because a rat may be entirely quiet during a determination, yet show an increased rate because of a fit of activity just before that determination began. In practice, our method of evaluating the primary data usually resulted in the selection of the lowest or the average of the several low metabolic rates determined during the course of the 4 to 7 hour period. These low determinations usually varied less than ± 4 per cent from their average, although the metabolic rates from week to week may show as much as ± 8 per cent variation from the average level in males and slightly more in females. The metabolic rates are expressed as calories per day per square meter of body surface.

A number of basal metabolic rate determinations were made for each rat before treatment with anterior lobe preparation was begun, in order to determine the normal basal level and the extent of the normal variations from the average. In 8 of the rats used, a long series of such control determinations had been made.

The growth promoting substances used were neutralized alkaline extracts of fresh beef anterior lobe, prepared after the method of Putnam, Teel and Benedict (9).* Daily doses of 1 cc. were injected intraperitoneally for periods ranging from 15 to 72 days. Two periods of treatment with extracts were given in 5 rats, separated by rest intervals of 18 to 55 days. Four lots of extracts which had been found to be potent in promoting growth in control rats were used. Of these No. 3 was the most potent and No. 4 the least, judging from the growth response elicited. The average growth increase in the experimental rats on extract No. 3 was also the greatest. Extracts Nos. 1 and 2 were about equally potent and a little less so than No. 3. The extracts were not given over a sufficiently long period to produce "giant" rats, and probably the rate of increase in weight was not the maximum possible, since there were at least two 24-hour starvation periods each week for metabolism determinations.

Two sources of the sex maturity or gonad stimulating principle were used. One was an extract of sheep anterior lobe prepared by Parke, Davis & Company, the other was prepared by ourselves from the urine of women in the first five months of pregnancy, after the method of Biedl (10). The potency of the extracts used was assayed by testing on infantile rats as described by Biedl. Various dosages were used in the metabolism experiments, ranging from ½ unit once or twice a day to 6 units daily in two doses.

Two experimental procedures were carried out with both the growth promoting and the gonad stimulating extracts, one to determine the immediate effects of the extracts on the metabolic rate, and the other to determine the effects of continued daily administration.

*We are indebted to Parke, Davis & Company for preparing and furnishing these extracts, and also the anterior lobe extracts containing the gonad stimulating principle.

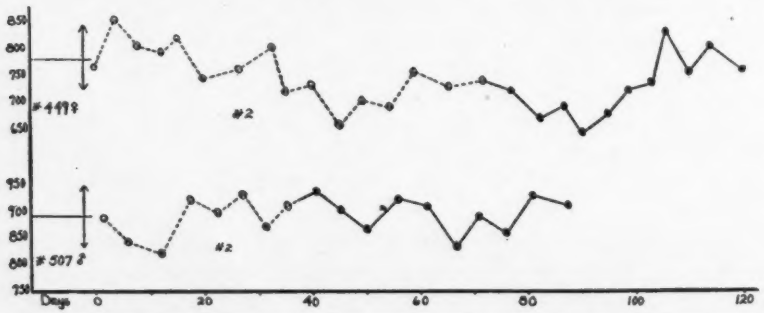
RESULTS

Growth Promoting Principle. In studying the immediate effects of the growth promoting extracts, doses of 1 or 2 cc. were given intraperitoneally either after a preliminary metabolic rate determination on the same day, or to rats in which the basal level had been well established. The metabolic rate was then followed for 3 to 6 hours. Eleven such experiments were made with 7 animals, 4 females and 3 males. In 9 instances there occurred a definite increase in the heat production over the average basal level. This increase ranged from 6 to 17 per cent with an average of 10 per cent, and reached its maximum in 2 to 4 hours after the injection of the extract. In 2 experiments there was no apparent effect in response to the injection. In 4 rats similar determinations, made after the injection of *boiled* extracts in which the growth principle was destroyed, showed an increased heat production over the normal basal of about the same magnitude (5 to 13 per cent).

Almost any material, even saline solution or distilled water, when injected intraperitoneally, will increase the metabolic rate (Baeq, 11), and protein has a well-known specific dynamic action. These extracts contained about 10 per cent of protein and we believe that the increased oxygen consumption observed within the first few hours after intraperitoneal injections of the growth extracts, may be due to the dynamic action of the protein products and to the solution.

In the experiments on the effects of continued daily administration of the extracts, 18 rats, 7 males and 11 females, were used. In this series at least 24 hours elapsed after the injection of the extract before a metabolic rate determination was made, in order to obviate any specific dynamic effect.

There was a considerable variation in the metabolic responses of these animals, but a significant increase in the basal level was not found in any rat of the series either during the periods of treatment or afterwards. In 5 females and 3 males, or 40 per cent of the whole series, the extracts were



1. Effect of growth promoting extracts on the basal metabolic rate. The heat production is expressed as calories per day per square meter of body surface. The average normal basal rate is shown at the beginning, with the range of the variations indicated by the double arrow. The period during which the extract was given is shown by the broken curve.

apparently without any metabolic effects and the rates remained at about the same average level before, during and after the period of administration. The greatest single variations from the average levels in these 8 rats were +14 and —11 per cent, but such occasional variations are probably meaningless. It is perhaps significant that of these 8 rats showing negative metabolic effects, all except one failed to show growth responses to the extracts. Three females and one male received extract No. 4, which was found to be the least potent in promoting growth. In Figure 1, the individual determinations on male rat 507 are graphed. Extract No. 2, given daily for 38 days, had no significant effect on the metabolic rate, except for a suggestion at about the twelfth day. The graph for this rat is fairly typical of those for the other 7 which showed no metabolic effects.

In 10 rats a significant decrease in the basal metabolic level was observed. In 4 females and 3 males this fall began during the period of administration of the extracts, but not until after several days' treatment had been given. In all experiments except one the metabolic rate fell to a lower level after the treatment with the extract had been stopped than while it was being given. In three rats the decrease did not occur until after the injections were stopped. In most cases the rate reached its lowest level in 6 to 18 days after stopping the extracts and then gradually rose again. This inertia in the metabolic response was a characteristic finding, and is suggestive of the metabolic response to thyroidectomy. The extent of the decrease for each rat is given in Table I, and the individual curves of 5 rats showing typical responses are given in Figures 1, 2 and 3.

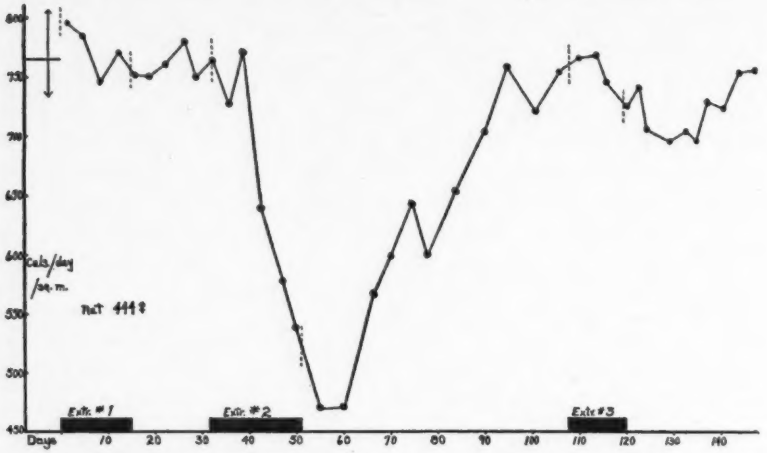
TABLE I

EXTENT OF LOWERING OF METABOLIC RATE IN RATS WITH GROWTH PROMOTING PRINCIPLE

Rat No.	Period of Treatment	Decrease During Treatment	Maximum Decrease After Treatment	Time Before Maximum Decrease
	Days	Per Cent	Per Cent	Days
500m	18	27	27	8
500m	18	?	None	..
505m	18	13	19	15
601f	18	None	16	8
601f	27	8	19	9
604f	48	None	18	14
444f	19	30	39	9
444f	11	?	10	9
449f	72	16	17	17
472m	26	12	16	12
17f	27	9	12	8
580m	23	9	11	15
455f	43	None	13	11

The most marked decrease in metabolic rate was shown by rat 444 (Figure 2). This female had an average normal metabolic level of 766 calories per day per square meter of body surface in 8 determinations, with extreme ranges of 735 and 807 calories. Extract No. 1 given daily for 16 days had no significant effect on the metabolic level either during the period or for 18 days afterwards (9 determinations). Extract No. 2

was then given for 19 days. Eleven days after the first injection, the metabolic rate was 640 calories—a decrease of 17 per cent. Seven days later it had dropped still further to 538 calories, or a decrease of 30 per cent from the normal basal level. The extract was then stopped and the rate in 4 days fell to 470 calories and 5 days later was found to have the



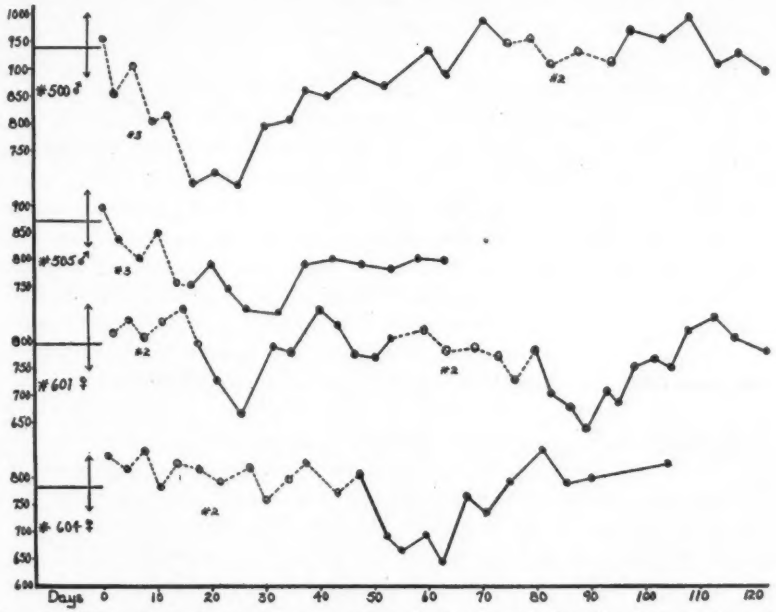
2. The effect of extracts Nos. 1, 2 and 3 on the basal metabolic rate of rat 444. The period of administration of the extracts is indicated by the heavy bars.

same value. This represents a decrease of 39 per cent from the original average level, and is the most extreme response we have found. There was then a slow, gradual increase in the metabolic rate, but apparently not to the original level. The few determinations made 6 to 8 weeks after extract No. 2 was discontinued would indicate that a new level had become established at about 740 calories. Extract No. 3 was then given for 11 days. It caused possibly a slight lowering of the metabolic rate. After stopping this extract the rate in 9 days fell to 694 calories and then in 14 days more gradually rose to about 750 calories.

Extract No. 2 was injected into female rat 449 (Figure 1), for 72 days. The average normal basal level was 778 calories. During the period with the extract there was a slight gradual lowering of the metabolic level. On the 45th day the lowest rate of 657 calories was recorded, or 16 per cent lower than the original level. This low level was not maintained, but after the injections were stopped, there was a further decrease for 17 days when the rate of 646 calories or —17 per cent was recorded. After this there was a gradual return in 2 weeks to about the original level.

Male rat 500 (Figure 3) showed a quick response to extract No. 3. Its average basal level in 7 determinations ranged from 883 to 1014 calories with an average of 940. One cc. of extract was given intraperitoneally for 18 days. Six basal metabolic rate determinations made during this period gave rates of 956, 853, 907, 805, 816 and 687 calories, or a maximum

decrease of 27 per cent. The injections were stopped and 8 days later the lowest rate of 685 calories or —27 per cent was recorded. There was then a gradual rise to approximately the original level over a period of 40 days. Extract No. 2 was then given for 18 days. There was no significant change either during or after the period of injection, although there is the suggestion of a fall in the rate during the time the injections were given.



3. Effect of growth promoting extracts on the basal metabolic rates of four other rats. Same conditions as in Figure 1.

Male rat 505 showed a response similar to but not so marked as that of 500 when given the same extract for the same length of time. The post-injection fall in metabolism continued for a longer time, 15 days. The lowest rate recorded was 703 calories or a decrease of 19 per cent from the original level of 871 calories. There was then a return to an apparently new and less variable level of about 800 calories. This rat acquired a pulmonary infection which prevented its being followed further.

Female 601, with a basal level of 793 calories, showed no decrease during an 18-day period of injection of extract No. 2. The 6 determinations made in this period, although higher than the average normal level, were all within 9 per cent of this level. Following the injection period there was a fall in 8 days to 668 calories or 16 per cent below the normal basal level. There was then a rise to approximately the original level in 10 days. The same extract was then given for 27 days and produced a slight lowering of the level. After discontinuance the rate decreased in 9

days to 642 calories, or —19 per cent, followed by a return in 16 days to about the original level.

Female 604, with an average normal level of 782 calories, showed a suggestion of an increased rate during 48 days of administration of extract No. 2. The highest rate recorded was 851 calories or only +9 per cent, however, and the preliminary basal level was based on only 3 determinations. In the post-injection period the rate fell in 14 days to 646 calories, or —17 per cent. It then rose in 15 days to a level of about 800 calories, which further suggests that the average level in the preliminary period is slightly low.

No significant changes were found in the respiratory quotients as a result of the growth promoting extracts. A total of 18 respiratory quotient determinations, during the period when extracts were given, showed an average value of 0.73, which is close to the average in control rats.

Gonad Stimulating Principle. Reiss and Winter (12), using extracts of the sex maturity stimulating principle from the urine of pregnant women, found no constant effects on the oxygen consumption, carbon dioxide production or respiratory quotient in rabbits. They used anesthetized animals, however, gave enormous doses (200 to 4000 units) of the material subcutaneously and followed the metabolism for only a few hours after each injection. We have used what are presumably more physiological doses, without anesthesia, and have followed the metabolic level during and after periods of continued daily administration. The results are given in Table II. Twelve rats were used, 9 females and 3 males. The extracts of gonad stimulating principle, both from anterior lobe and from the urine of pregnant women were given in doses of 1 to 6 rat units per day for 8 to 24 days. Frequent metabolism determinations made during and

TABLE II

EFFECTS OF GONAD STIMULATING EXTRACTS ON METABOLIC RATE

Rat No.	Average Normal Basal Level	Gonad Stimulating Principle		Average Basal Level During Treatment	Average Basal Level After Treatment
		Units/Day	Days		
	Cals./Day/Sq. M.			Cals./Day/Sq. M.	Cals./Day/Sq. M.
		Anterior Lobe Extracts			
280f	786	4	8	831	813
8f	717	3	9	740	704
477f	807	4	9	792	783
65f	752	1	9	740	745
20m	907	4	9	920	892
557m	840	2	8	835	815
		Urine Extracts			
477f	783	3	15	776	759
450f	767	1	24	797	782
400m	774	3	24	785	766
355f	642	5	11	691	658
105f	701	4	11	742	710
401f	732	6	24	761	745
23f	681	4	24	660	665
557m	815	5	11	819	803
Average	765			778	760

after the period of treatment showed no significant changes from the normal level. The total average of the metabolic rates during the period of treatment was only 2 per cent higher than the normal average rate. Twenty determinations were made immediately following the subcutaneous administration of the extracts in doses of 2 to 8 units. Here again there was no significant change in the metabolism, although the tendency was towards an increased rate. The average rate in the 3 to 5 hours after injection was only 5 per cent higher than the normal average level.

DISCUSSION

The decrease in the metabolic rates as a result of the growth extracts does not seem to be sufficiently uniform to warrant the conclusion that the anterior lobe has an anti-calorigenic function. Although none of the rats showed an increase in metabolic rate, only 60 per cent showed significant decreases, and the responses in these varied from —10 to —39 per cent. There was apparently some rough correlation between the potency for growth promotion and the metabolic action. Extract No. 4, which was the least potent for growth, had no effect in 4 rats and only a slight metabolic effect in others. Extract No. 3, which was the most potent for growth, caused in every instance a fall in the metabolic level. Rat 444, however, showed a marked response to extract No. 2 and a much lesser response to No. 3.

The inertia of the metabolic response to the extracts was characteristic, the fall in rate beginning several days after the first dose of the extract, and continuing for some days after the injections were stopped. The growth response is also a slow one in rats, but apparently ceases within a day or so after the administration of the extract is stopped. Even with definitely potent extract, not all of the rats in a series show augmented growth rates and the same seems to be true of the metabolic response. The data are not sufficient to determine whether or not the effect on the metabolism is cumulative.

In general, the results substantiate those obtained in giant rats (13), in which the metabolic levels were found to be about 13 per cent lower than normal. They are also compatible with the results reported by Teel and Watkins (14), who found in dogs a marked drop in the non-protein nitrogen of the blood, and a decrease of urea and amino acids after injection of growth-promoting extract.

Without further data it is unprofitable to speculate as to the mechanism by which the growth-promoting extracts can cause a fall in the general metabolic rate. A number of bits of evidence, however, indicate that the thyroid may play some rôle in the mechanism, and further experiments along this line are being undertaken.

Our results with the gonad stimulating extracts supplement the observations of Reiss and Winter (12) on rabbits and indicate that in rats this material is without any general metabolic effect.

SUMMARY

In adult rats the subcutaneous injection for periods of 8 to 24 days of 1 to 6 rat units per day of the gonad stimulating principle of the anterior lobe of the pituitary had no significant effect on the basal gaseous metabolic rate. Extracts both of fresh anterior lobe and of urine from women in the early half of pregnancy were used.

Ten rats of a series of 18 given daily intraperitoneal injections of growth-promoting extracts of anterior lobe for 15 to 72 days showed significant decreases in the basal metabolic levels ranging from 10 to 39 per cent. Eight rats showed no metabolic response. None of the animals showed an increase in the metabolic rate except when the determinations were made within a few hours after intraperitoneal injections. The fall in the metabolic rate appeared usually only after several daily doses of the extract had been given, and in most cases continued for 6 to 14 days after treatment with the extract had been stopped. Approximately the original levels were regained by most rats within 6 weeks.

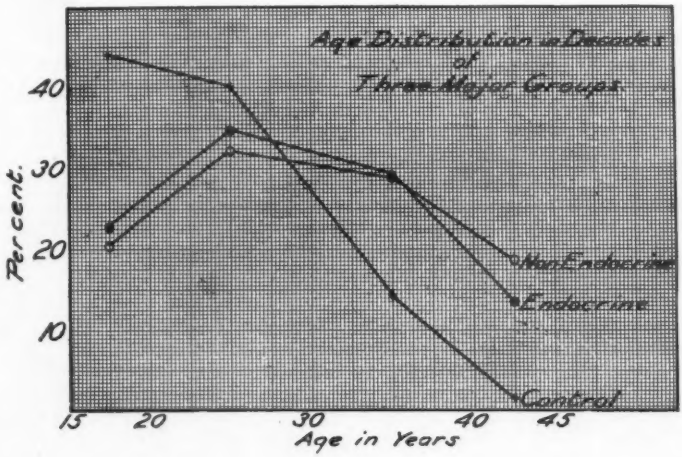
BIBLIOGRAPHY

1. Raab, W.: Klin. Wchnschr. **7**: 1381, 1430. 1928.
2. Rowe, A. W. and C. H. Lawrence: This Journal, **12**: 245. 1928.
3. Falta, W. and F. Högler: Wien. klin. Wchnschr. **43**: 378. 1930.
4. Aub, J. C.: J. A. M. A. **79**: 95. 1922.
5. Boothby, W. M.: J. A. M. A. **77**: 252. 1921.
6. Benedict, F. G. and J. Homans: J. Med. Res. **25**: 409. 1912.
7. Zondek, B.: Klin. Wchnschr. **9**: 245. 1930.
8. Benedict, F. G.: J. Nutrition **3**: 161. 1930.
9. Putnam, T. L., H. M. Teel and E. B. Benedict: Am. J. Physiol. **84**: 157. 1928.
10. Biedl, A.: Endokrinologie, **2**: 241. 1928.
11. Bacq, Z. M.: Ann. de physiol. **5**: 349. 1929.
12. Reiss, M. and K. A. Winter: Endokrinologie, **3**: 174. 1929.
13. Lee, M. O., H. M. Teel and J. Gagnon: Proc. Soc. Exper. Biol. & Med. **27**: 23. 1929.
14. Teel, H. M. and O. Watkins: Am. J. Physiol. **89**: 662. 1929.

ENDOCRINE STUDIES. XXVI. AN ENDOCRINE INFLUENCE ON MENSTRUATION*

ALLAN WINTER ROWE, PH.D.
Evans Memorial,
BOSTON, MASS.

It has long been recognized that the age of onset of the catamenia, together with the rhythm and amount after establishment, are all greatly influenced by a number of constitutional factors. Among these regulatory mechanisms the glands of proven internal secretion, in more recent years, have tended to assume an increasing significance. That ovarian function is important may be taken for granted, but the activities of both the pituitary and thyroid glands are now generally recognized as also real influences in determining the menstrual picture. The pancreas is omitted purposely from the present review but Joslin (1) notes a depressing effect of diabetes on menstruation and the occasional correction of amenorrhoea under insulin therapy. Both the adrenals and parathyroids are likewise excluded, since the number of proven cases we have seen is far too few to permit of informative statistical analysis. The endocrine significance of the thymus, pineal and spleen are, at best, questionable, and they find no place in the present discussion.



This paper deals with the correlation of menstrual disorders with a variety of disturbed endocrine functions and with certain disease states not primarily associated with the ductless glands.

*Read before the Fourteenth Annual Meeting of the Association for the Study of Internal Secretions, Detroit, Michigan, June 23, 1930.

The cases used for the study were selected from the records of a consecutive series of patients who had been carefully investigated by a diagnostic programme, described in detail elsewhere (2).

The data from all of the female patients between the ages of 15 to 46 have been collated, young children and women past the climacteric only being excluded. The composition of the several etiological groupings can be presented most compactly in tabular form.

TABLE I
GROUP COMPOSITION

Group	Married	Unmarried	Total
Pituitary	149	193	342
Thyroid	98	108	206
Ovary	121	139	260
Total Endocrine	368	440	808
Non-Endocrine	203	223	426
Controls	250	275	525
Grand Total	821	938	1759

The pituitary cases were divided as follows: hyperfunction, 0.9%; dysfunction, 76.3%; and hypofunction, 22.8%. Similarly, the thyroid distribution was 8.7%, 32.5% and 58.8%, respectively. The ovarian cases were all hypofunctional. Group analysis in case of the first two series failed to disclose significant variations that might be attributed to different function levels.

But few words of explanation are necessary. The relatively predominance of ovarian cases in the endocrine group (nearly 1/3*) is due to the fact that practically all of the gonad cases are in women, while groups of pituitary and thyroid cases show a very significant male representation. Further, as has been pointed out elsewhere (2-d), ovarian failure is seemingly confined to the years of maturity and thus young children have no part in the series.

The control group was made up of a series of young, unmarried women demonstrated to be normal by a searching physical examination and negative medical history. In addition, as the pathological groups comprised both married and unmarried women, and as the marital state is conceded to exercise some influence on the catamenial picture, a second control group was made up of a series of normal and demonstrably healthy, pregnant women drawn from the Maternity Service.

It will be noted that the distribution of married and unmarried subjects throughout the several sub-groups is about the same, hence any special influence of sexual activity is represented uniformly.

The "non-endocrine" group is composed of patients presenting initial suggestions of some hormone defect in history or physical examination but demonstrating on careful examination both an absence of endocrine involvement and the presence of some concrete disease state. The etiological scatter is a wide one, and the component members of the group are given in the next table (Table I-a).

*The usual incidence in a complete series approximates 5:3:2 for Pituitary, Thyroid, and Gonads, respectively.

TABLE I-a
ANALYSIS OF NON-ENDOCRINE GROUP

Group	Sub-Group	Number
Infections	Tuberculosis, Arthritis, Primary Focal	45
Mental and Nervous Disorders	Neuroses, Psychoses, Psycho-neuroses	54
	Central Lesions, Epilepsy, Parkinsonians, Mental Retard, Miscellaneous	60
Disorders of Metabolism	Obesity, Malnutrition, Gout, Bone Diseases	27
Cardio-vascular Disorders	Cardiac, Renal, Cardiorenal	41
Blood Diseases	Primary Anaemia, Leukaemia, Haemophilia	9
Tumors	Malignant, Benign, Non-toxic Goiter	21
Disorders of	Eye, Ear, Skin, Allergy, Gastro-intestinal	78
Syphilis		25
Hepatic Dysfunction		43
Pelvic Disorders		12
Normal Controls		11
	Total	426

The ages of the patients were conditioned naturally by the onset and development of their presenting difficulties; equally, those of the married controls by the occurrence of the current pregnancy. The unmarried controls were drawn from groups of nurses and college students and, in the main, were under thirty years of age. The age distribution is represented graphically in the accompanying diagram.

A larger number of the control group were less than thirty years of age than was the case in both the endocrine and non-endocrine series; these latter showed an excellent correlation with each other. That the discrepancies of the control group were more apparent than real is shown by the average ages of each series, which were as follows: Pituitary, 28.6 years; Thyroid, 28.5 years; Gonad, 29.1 years, or for the combined Endocrine group 28.7 years. The average for the non-endocrine series was 29.8 years, and for the control group 24.1 years. The data, therefore, may be regarded as reasonably comparable.

In considering the age of onset of the catamenia it must be remembered that many of the endocrine and non-endocrine patients had certainly developed their presenting conditions in the years following the establish-

ment of menstruation. For this reason the figures recorded must be regarded as minima, and slight tendencies assume a significance disproportionate to their actual numerical values. To secure really authoritative data on this point it would be necessary to observe a series of children with active endocrine disturbances from prepubertal years until the time of maturation, recognizing further that in an appreciable number the spontaneous correction of the endocrine disorder would allow an onset of the catamenia at a conventionally normal age. From another standpoint this latter fact also is a factor in the reported late onset with individuals who present no active endocrine involvement at the time of examination. An earlier endocrine disorder may determine a delayed catamenia and then itself disappear, leaving apparently a normal function level. The whole problem of pelvic hypoplasia is intimately connected with this question as it is with that of sterility in later years.

Another uncertainty lies in the designation of the "normal" age for the catamenial onset. The literature is rich in conflicting observations, diet, climate, race, social conditions, and other factors superimposing active influences upon what may more strictly be designated as constitutional. In the wealth of anthropological data collected by Ploss and Bartels (3), every age from ten to eighteen seems to prevail as characteristic in individual selected groups. That the average for Caucasians dwelling in North America is somewhat lower than for the same racial strains in Europe would seem to be established. With the uncertainty existing as to the norm, it may be permissible to include here the records from this series as additional data bearing on the problem. All the patients in the present study were "Americans," i. e., Caucasians living in the United States, and with few exceptions were native born. The distribution, reduced to per cent for ease of comparison, is given in the next table (Table II).

TABLE II

AGE OF ONSET OF CATAMENIA

Group	9	10	11	12	13	14	15	16	17	Over 17
Pituitary	0.6	1.8	7.2	19.5	33.7	19.8	7.2	6.3	2.4	1.5
Thyroid	1.0	1.5	8.3	16.6	33.7	21.5	6.8	5.8	2.4	2.4
Ovary	0.	0.	6.2	18.2	30.6	27.5	8.8	4.3	2.7	1.7
Total Endocrine	0.5	1.3	7.2	18.3	32.7	22.7	7.7	5.5	2.5	1.6*
Non-Endocrine	0.	1.4	6.6	15.2	31.6	26.5	9.7	5.2	2.4	1.4*
Control	0.	0.6	4.9	16.7	30.5	27.9	10.4	5.9	1.3	0.8*

*17 at 18, 6 at 19 years.

The coincidences are more striking than the divergences. Three in every four in each of the three major groups matured between the twelfth and fifteenth birthdays, and again in each series over 90 per cent had established the menstrual function before sixteen. With just allowance for the relative values, it seems fair to assume that the function not established before sixteen, and less certainly before fifteen, may be regarded as delayed in onset. In other words, failure to mature by fifteen suggests the need of consideration, and by sixteen requires it.

No endocrine influence can be deduced from these data. While it is true that the percentage of endocrine subjects maturing after the eighteenth birthday is twice that of the control group, the average age of the latter within the conventional normal limits is somewhat higher than that of the former; the weight of the non-endocrine series approaches that of the control group. The average age of 13.5 years agrees well with the 13.9 years of Engelmann (4).

While the data from the mature cases fail to disclose any significant endocrine influence, the two points previously noted, *i. e.*, the onset of the endocrinopathy after maturity and the spontaneous correction of a prepubertal endocrine defect before or after the conventional age of onset, must not be forgotten. One is warranted only in the conclusion that data of the character given in Table II are not adapted to throw light on the question of an endocrine influence during the crucial years.

Somewhat more significant are the records of those patients who have failed to mature, although examined at an age when an established function might normally be expected. The present series contains a few such, and the significant facts are collected in the next table.

TABLE II-a
MATURITY FAILURE
(All Patients from 15 to 25 years inclusive.)
NON-ENDOCRINE ETIOLOGY

Group	Number	Not Matured		
		Number	%	Ages
Pituitary	110	8	7.3	15, 15, 16, 17, 17, 18, 20, 24
Thyroid	78	1	1.3	17
Ovary	100	0	0.	
Non-Endocrine	125	5	4.0	15, 16, 16, 18, 21

Non-Endocrine Etiology

	Ages
Two with Congenital Syphilis	16, 21
One with Tuberculosis	18
Two with Lesions of the Central Nervous System	15, 16

The inclusion of the cases at fifteen years is perhaps arbitrary, but their deletion would not affect the significance materially.

On the basis of chronological age only three, two pituitary and one non-endocrine case, exceed the upper limit of the control group. All of the patients in this list, however, gave numerous evidences of a retarded physical development other than failure of menstruation. The absence of ovarian cases rests upon the observation already noted that a primary failure of ovarian endocrine activity is seemingly an incident only of the years of maturity.

The figures given above warrant the conclusion that endocrine malfunction in the earlier years may produce a retardation of sexual development seemingly through a depressing influence on general growth activities. A similar influence is patently exercised by certain other conditions not demonstrably associated with the ductless glands. Parenthetically it

may be said that precocious puberty seemingly arises from hormone disturbances—the figures in Table II offer a very modest support for this thesis—but the dubious endocrine significance of certain of the alleged causal agents renders an exact allocation impossible at present.

With the menstrual function established, two characteristics demand consideration, *i. e.*, the interval of recurrence or rhythm of the period and the amount. Considering the first, it is generally recognized that the 28-day interval from the onset of one to that of the next period is characteristic. Equally, deviations from this accepted standard are frequently reported by seemingly normal women. An excellent review of the earlier literature is given by Novak (5), and the common report is of general regularity in from 70 to 75 per cent of the several series which have been investigated. Kelly (6) alone offers a significant exception in a record of 942 women of 1000 examined with a regular 28-day interval. In the figures quoted, regularity of function at an interval departing from the classic 28-day rhythm must be included. Taking the control group as a standard for later comparison, the data are collected in the next table (Table III).

TABLE III

CONTROL GROUPS

Type	Rhythm					
	Nulliparous		Parous		Total	
Regular						
26, 27	5		7		12	
28	197	218	144	202	341	420
29, 30	16		51		67	
Less than 26	15	24	15	18	30	42
More than 30	9		3		12	
Irregular*						
Diminished	7		5		12	
Both	9	33	7	30	16	63
Increased	17		18		35	

*In three cases irregular only in summer.

Menstrual irregularities are about equally common and similar among married and unmarried women, but the interval averages slightly longer in the married. Seventy-four per cent of the total control group show a regular 28-day interval, and 14 per cent more, regularity, but with a spacing greater or less than the mode. The fact that each person in the control group was demonstrated to be in good physical condition presumably accounts for a reported incidence of regularity higher than that noted in general community records.

Of possible irregularities there are obviously three types, with intervals diminished, intervals increased, and that form in which there is complete irregularity, both increase and diminution appearing in the interval as reckoned over a series of months. In the control group, increase in the interval is more frequent than the sum of the other two disturbances.

On the basis of the standards established by the control group, the data for the other series can be resolved and collected.

TABLE IV

RHYTHM OF PERIOD

Group	Interval			
	Regular	Irregular		
		Diminished	Both	Increased
Pituitary	59.3%	9.9%	3.0%	27.8%
Thyroid	50.0%	12.6%	17.5%	19.9%
Ovary	59.6%	9.7%	3.1%	27.5%
Total Endocrine	57.0%	10.5%	6.8%	25.7%
Non-Endocrine	73.9%	7.6%	4.3%	14.2%
Controls	88.0%	2.3%	3.0%	6.7%

Here for the first time an unmistakable endocrine influence can be traced. This is patently referable to the fact that the menstrual habit and the endocrinopathy are observed coincidently and thus the errors unavoidable in the data on "onset" are eliminated. All of the endocrine series show a regularity significantly below the other two series—the thyroid the lowest at 50 per cent—and also below the usual report which is practically that of the non-endocrine group. Of the irregularities, the pituitary and ovarian groups show a dominant tendency toward a lengthened interval, the ratio to an abbreviation being 3 to 1. Only the thyroid shows a significant figure for the group showing complete irregularity, the cases indicating it nearly equalling in frequency those with delayed interval. This is a unique datum and defines a tendency characteristic of thyroid disorders which has been previously recorded (2-c). Where irregularity occurs the prevailing tendency is patently toward increase in the interval as the figures for all of the major series testify. To summarize, endocrine disorders tend to render the rhythm irregular with an increase in the interspace as the common expression. Thyroid disorders alone tend to produce a complete irregularity from four to six times as frequently as in the other series.

The amount of the period is less susceptible to exact expression. Both the duration in days and the amount of the flow come into consideration, and while the first can be reported with some degree of accuracy, estimation of the second scarcely falls in the realm of objective data. The personal hygiene and esthetic reaction of the individual influence so largely the number of napkins—the usual standard of measurement—as to make the report of but dubious significance.

Dealing first with the period duration in days, the reports in the literature (see Novak l.c.) show a wide scatter from the 4-5 day period of one group to the 2-8 allowance of another. That data should be comparable even though the limits selected be conventional and in some degree

arbitrary, an analysis has been made of the present control group reports and the final figures collected in the next table (Table V).

TABLE V
DURATION

Days	Control Groups					
	Nulliparous		Parous		Total Number	
Less than 2	0		0		0	
2	2	7	10	16	12	23
2–3	5		6		11	
3	24		39		63	
3–4	19		19		38	
4	57		53		110	
4–5	38	248	29	205	67	453
5	67		39		106	
5–6	19		13		32	
6	24		13		37	
6–7	3		2		5	
7	12	20	21	29	33	49
Over 7	5*		6†		11	

*Four at 8, one at 8–10.
†Five at 8, one at 7–8.

The distribution here shows that the great majority of cases fall between the lower limit of an established 3-day period, and the upper boundary of not over six days. It is clearly recognized that these limits are arbitrary—for example, the seven-day report almost equals in number that for six days—but the abrupt changes in the curve make the limits selected reasonable. As all comparisons are relative and an absolute standard of the normal not yet established, the limits selected are serviceable since they apply equally to all the series under consideration. The combined data are given in Table V-a.

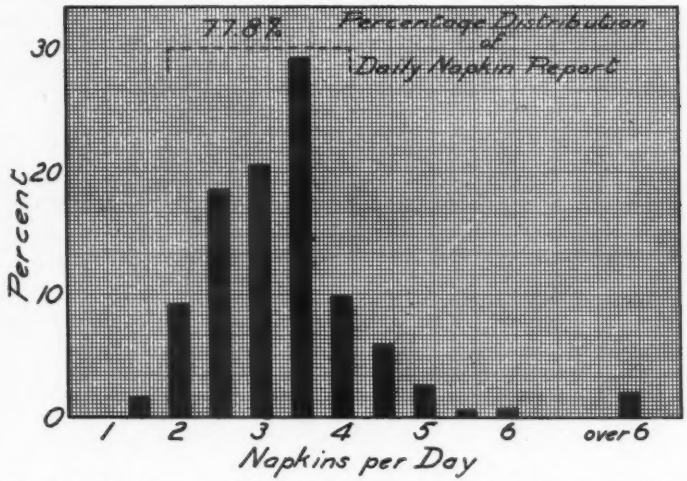
TABLE V-a
DURATION

Group	Less Than 3 Days	3–6 Days	More Than 6 Days
Pituitary	12.3%	74.7%	13.0%
Thyroid	14.9%	73.2%	11.9%
Ovary	13.0%	69.2%	17.8%
Total Endocrine	13.2%	72.3%	14.5%
Non-Endocrine	10.2%	71.3%	18.5%
Control	4.4%	86.3%	9.3%

Both the endocrine and non-endocrine groups show a lower incidence of cases with conventionally normal duration than does that of the controls. The endocrine cases show an equal tendency toward diminution and increase, while the non-endocrine group emphasizes the latter type. A true endocrine influence is not clearly demonstrated by this datum but the facts point to a lowering of the frequency of normal duration through metabolic derangements arising from a wide variety of causes.

As was noted above, the actual quantity of the flow is influenced by so many extraneous factors as to be incapable of any exact estimation.

Analysis of the data from the control series, however, on the basis of the napkin report would seem to indicate that the majority of those composing the series use from eight to sixteen napkins per period. The accompanying graph illustrates the several habits in terms of number (Plate 2).



Such a division is arbitrary and thus open to criticism. The standard has the same degree of authority as that for duration, and as it affects all the series alike, with just recognition of the intrinsic limitations, it may be adopted as a first approximation.

TABLE VI
AMOUNT OF FLOW

Group	Fewer Than 8 Napkins	Over 16 Napkins
Pituitary	20.8%	19.0%
Thyroid	27.5%	17.6%
Ovary	26.0%	26.0%
Total Endocrine	24.2%	21.4%
Non-Endocrine	17.1%	23.2%
Control	9.0%	14.2%

The figures here repeat in fair measure the indications already noted under the duration of the period. Both of the disease groups show a significantly larger percentage of cases falling either above or below the arbitrary normal standard. The endocrine group shows a slightly larger proportion of abnormal cases than its non-endocrine fellow, and with the tendency somewhat toward a scanty rather than a profuse flow. Again, the departures could as well be assigned to general poor health as to a specific endocrine agent.

The true measure of the period lies in the combination of the duration and the amount. A three-day period with four well-used napkins

daily approaches far more closely the normal standard than does a six-day flow which spots but one napkin a day. Further, the individual woman has criteria of performance based on her personal experience and that of her circle of friends, which merit consideration. In obtaining these data effort has been made to secure the opinion of each patient on her personal performance as well as the numerical data which have just been discussed. Collating the information from these several sources, the final figures are collected in the next table.

TABLE VII
PERIOD ANALYSIS

Group	Decreased	Normal	Increased
Pituitary	29.0%	50.3%	20.7%
Thyroid	28.2%	53.9%	17.9%
Gonad	23.0%	53.7%	23.3%
Total Endocrine	26.9%	52.3%	20.8%
Non-Endocrine	27.1%	57.9%	15.0%
Control	9.1%	75.8%	15.1%

Considering that the criteria are uniformly applied throughout, these figures have some significance even though the sources from whence they derive are not to be regarded as unimpeachable.

The endocrine influence is unmistakable even though the effect of non-endocrine disease runs it a close second. In both the disease groups the prevailing tendency is toward a scanty period, an indication deriving added emphasis from the fact that the control group shows the opposite tendency. The figures as given are informative; they require no elaboration; an endocrine influence tending to produce abnormality would seem to be established.

There remains but one more consideration and that deals with the most subjective datum of the entire group.

Dysmenorrhea is a highly elastic term and its report of presence and degree depends upon widely varying individual standards. Taking the report of severe dysmenorrhea as the criterion, the occurrence in the several groups is as follows:

TABLE VIII

Group	Positive Report	Summary
Pituitary	17.5%	25.6%
Thyroid	18.5%	
Ovary	42.0%	
Non-Endocrine		26.7%
Control—Nulliparous	13.1%	8.0%
Control—Parous	2.4%	

The several indications are interesting. The higher value for the unmarried as opposed to the married controls accords well with the generally recognized influence of an active sex life. Together, the control group

shows but one-third of the frequency of report of either of the other two major series. Considered individually, dysmenorrhea is less frequently found in patients with pituitary or thyroid disease than in those with a variety of non-endocrine complaints although reported twice as often as by the control group. The large number of cases reported in the ovarian series is but one more expression of the egocentric nervous instability which characterizes the sufferers from ovarian failure.

CONCLUSION AND SUMMARY

1. The menstrual histories of groups of women demonstrating three major endocrinopathies, pituitary, thyroid, and ovary, of a similar group presenting a variety of non-endocrine complaints, and of a control group comprising healthy married and unmarried females, have been analyzed.

2. Data obtainable by this method are not adapted to indicate the presence or absence of an endocrine influence on the age of onset of the catamenia. The reasons for this are indicated. An analysis is given showing that among Caucasians resident in the United States, the sixteenth birthday, and less certainly the fifteenth, may be regarded as the latest normal age for the establishment of the menses.

3. The few patients in the entire series who have failed to mature at an age when menstruation normally would be established, serve to indicate an active influence of the pituitary on menstruation.

4. An unmistakable endocrine influence is demonstrated in the determination of the rhythm of the function, all of the endocrinopathies tending to produce irregularity, with the prevailing type exhibiting an increase in the interval. The thyroid cases show a unique frequency in the report of a complete irregularity which may be regarded as characteristic.

5. Examination of the reports from the control group establishes a period of from three to six days, and an amount requiring from eight to sixteen napkins as the prevailing mode. On this basis the endocrine cases show a significant departure from the norm, which is only less strikingly exhibited by the non-endocrine series.

6. Any disease state seemingly increases the report of dysmenorrhea, the frequency being in the order of ovary, non-endocrine, thyroid, and pituitary disorders. The relatively high frequency of reports of dysmenorrhea in cases of ovarian deficiency undoubtedly derives in part from the marked nervous instability associated with the condition.

The writer wishes to express his thanks to Miss Mary McManus for assistance in compiling the data of the control group.

BIBLIOGRAPHY

1. Joslin: "Treatment of Diabetes Mellitus." 1928. Lea & Febiger, Phila.
2. (a) Rowe: This Journal, **12**: 1. 1928.
   (b) Rowe and Lawrence: Ibid. **12**: 245. 1928.
   (c) Lawrence and Rowe: Ibid. **12**: 377. 1928.

(d) Rowe and Lawrence: Ibid. **12**: 591. 1928.
(e) Lawrence and Rowe: Ibid. **13**: 1. 1929.
(f) Rowe and Lawrence: Ibid. **12**: 707. 1928.
(g) Lawrence and Rowe: Ibid. **13**: 109, 263. 1929.
(h) Rowe: Ibid. **13**: 327. 1929.

3. Ploss and Bartels: (v. Reitzenstein) "Das Weib." 1927. 11th Ed. Neufeld & Henius, Berlin.
4. Engelmann: Tr. Am. Gynec. Soc. **26**: 77. 1901.
5. Novak: "Menstruation and its Disorders." 1921. D. Appleton & Co., New York.
6. Kelly: "Medical Gynaecology." 1908. D. Appleton & Co., New York.

LIGATION OF THE TAIL OF THE PANCREAS IN JUVENILE DIABETES*

GÉZA DE TAKÁTS, M.D., M.S., F.A.C.S.
CHICAGO

The regenerative power of the pancreas has been established by numerous clinical observations. Of all structures the ducts and islets are most resistant to local destructive processes and seem to have the greatest growth potential. Various pathological conditions, such as luetic pancreatitis of the newborn, acute pancreas necrosis and carcinoma of the pancreas destroy a great deal of pancreatic tissue. External secretion may suffer or completely subside in some of these conditions, as for instance in a carcinoma of the head of the pancreas, with compression of the duct. Whether the insular activity is insufficient or not will depend on the rapidity with which pancreatic destruction takes place. Thus in acute pancreas necrosis, high blood sugars and abnormal sugar tolerance curves are almost a rule, and glycosuria not uncommon. Gradually, however, sugar tolerance returns to normal (Jorns, 1; Sebening, 2). In Sebening's series all cases of acute pancreas necrosis showed a normal sugar tolerance at the end of six months. Sprengell (3) saw the hemorrhagic pancreas necrosis at operation and removed a large sequestrum of pancreatic tissue. When ten months later the patient died of an acute intestinal obstruction, only a slight fibrosis in the body of the pancreas indicated the residue of previous destruction. The patient was sugar free. Histologically there were numerous and very large islands. Knopfloch (4) reported the autopsy of an eighty-two-year-old patient, who had had an acute pancreas necrosis forty years before. There was a marked atrophy and lipomatosis of the organ, which could be explained by the findings of concrements in the ducts which obstructed external secretion. In the lipomatous organ, intact, well preserved islands were numerous. There was no glycosuria.

The loss of external secretion does not interfere with islet function. Recent post mortem observations of Baló and Ballon (5) emphasized the irritative action of retained pancreatic juice on the hypertrophy of islet tissue.

In patients afflicted with a carcinoma of the head of the pancreas, glycosuria is seldom observed and then only temporarily (Elösser, Kehr, Germershausen, 6). In Koch's case (6) the scirrhous carcinoma surrounded or pushed aside the islets but did not invade them. Distally to the tumor the pancreas was small and fibrotic. The islands were numerous and well preserved. Jorns (1) published four cases of primary carcinoma of the pancreas, verified by laparotomy, in which sugar tolerance curves are available. Two patients showed a normal alimentary hyperglycemia, one

*Read before the Fourteenth Annual Meeting of the Association for the Study of Internal Secretions, Detroit, Michigan, June 23, 1930.

patient with bone metastases and cachexia showed a slightly diminished tolerance curve. The fourth patient showed a normal fasting blood sugar and a hypoglycemia following ingestion of sugar (61 milligrams per 100 cc. at 45 minutes and 56 milligrams in two hours).

I have tabulated twenty-eight cases of carcinoma of the pancreas seen at Wesley Memorial Hospital, Chicago, between 1910 and 1930, verified by operation or autopsy. A glycosuria was present in only one case, that of a very obese patient who obviously had a true diabetes mellitus. Through the courtesy of Dr. R. H. Jaffé I was enabled to study two additional cases of carcinoma of the head of the pancreas. Both showed a complete atrophy of the acinar tissue with well preserved islets and proliferating ducts. There was no glycosuria in either of them (Fig 1). Even of more interest is a case of Dr. S. W. McArthur's of St. Luke's Hospital, Chicago, because the diagnosis of pancreatic carcinoma was made at exploration and verified later by autopsy. It was possible to obtain a normal sugar tolerance curve after the operation (Fig. 2) which is remarkable, as the autopsy (Case No.

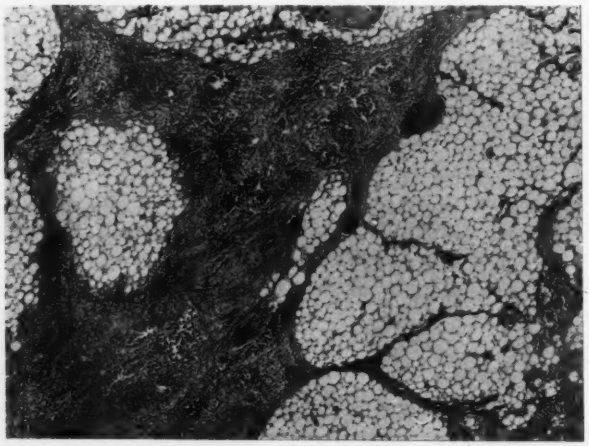


Fig. 1—Lipomatosis of the tail of the pancreas with intact islands surrounded by strands of connective tissue. Case of Dr. R. H. Jaffé, Cook County Hospital.

15—1929, St. Luke's Hospital, Dr. Paul Breslich) revealed that the pancreas was converted into a tumor mass with the exception of a small segment at the head of the gland. These cases will be published in detail elsewhere.

The foregoing data seem to indicate an ample reserve capacity and regenerative power of the *human* pancreas. I have purposely emphasized them, as *experimentally* a hypertrophy and hyperplasia of islet tissue has been recognized and reproduced repeatedly. In a previous communication the literature on this subject was summarized (7). A great number of previous investigators have found that ligation of the pancreatic duct will result in atrophy of the secreting parenchyma, with a perseverance and

occasional hypertrophy of islet tissue. The idea, however, of turning the tail of the pancreas into a ductless gland by interrupting its external secretion and using the head and body of the gland to secrete pancreatic juice, belongs to Mansfeld (7).

In our own experimental work, an atrophy of the secreting parenchyma was induced by a ligature or complete separation of the tail. We showed histological evidence of a hypertrophy and hyperplasia of the islet tissue (8), a rapid cessation of the external secretion from the separated tail (9) and, corresponding to the histologic findings, an increased carbohydrate utilization (10). The increased sugar tolerance occurred three to four months after the operation and gradually subsided in the normal dog within the first year. Possible reasons for a lack of persistent increase in sugar tolerance has been discussed in a previous article (10).

I have mentioned adequate clinical evidence that patients of middle and advanced age show a remarkable regenerative power of the pancreas when the gland is suddenly or gradually destroyed by local processes. There is also experimental proof of a morphologic and functional hyperactivity of the pancreas when its tail is ligated. The question naturally arose, whether hypertrophy and increased islet function could be brought about in a case of diabetes. The islet hypertrophy might not occur in diabetes, and even if it did, the new islet cells might succumb to the same agent as the original cells. That a clinical trial became possible is solely due to Dr. Russell M. Wilder, Professor of Medicine at the University of Chicago, whose continuous support and encouragement materially aided the experimental work, and who selected from his large number of diabetic patients two diabetic children. The difficulties of management in juvenile diabetes were described by Wilder and his co-workers on a material of 190 diabetic children (11).

In a preliminary report with Wilder (12), we pointed out that children with severe diabetes, whose dietary and insulin control was precise and whose diabetes after the initial fluctuations had become stationary or progressively worse should be selected for operation. Accordingly, the first case was selected. I can now report on the later results in this case and add the second case, in which a modification of the original operation was carried out eight months ago.

Case No. 1. Thomas M., age 13 [detailed history in a previous communication (11)] fell early in September, 1921, and hit the back of his head on a cement pavement. He was apparently well the following day, but a month later began to urinate frequently. Next day large amounts of sugar were found in the urine. The blood sugar was said to be very high. A restricted "Joslin type" of diet was instituted. A month later the child shrieked with abdominal pain (acidosis?). A second physician then instituted the "Allen type" of diet. In February, 1922, the child was sugar free on a liberal diet. However, a mild attack of influenza and later a second bump on the head brought on sugar in the urine in large amounts.

From March 24, 1923, to January 1, 1929, the patient had six admissions to the Mayo Clinic. In 1923 he was 48 inches tall, weighed 44 pounds, was weak and emaciated. With a dextrose value of 100 he received 15 units of insulin. At the second admission the insulin had to be increased to 20 units. At the third admission, the blood plasma carbon dioxide combining power was 34 per cent by volume. The insulin requirement reached 40 units. This was in August, 1924. Later he developed an acidosis because of an abscessed tooth and infected tonsils. On July 5, 1927, the dextrose value of his diet was increased to 120, with 40 units of insulin. At his admission to Wesley Memorial Hospital on January 20, 1929, the patient had been steadily taking 40 units of insulin and taking

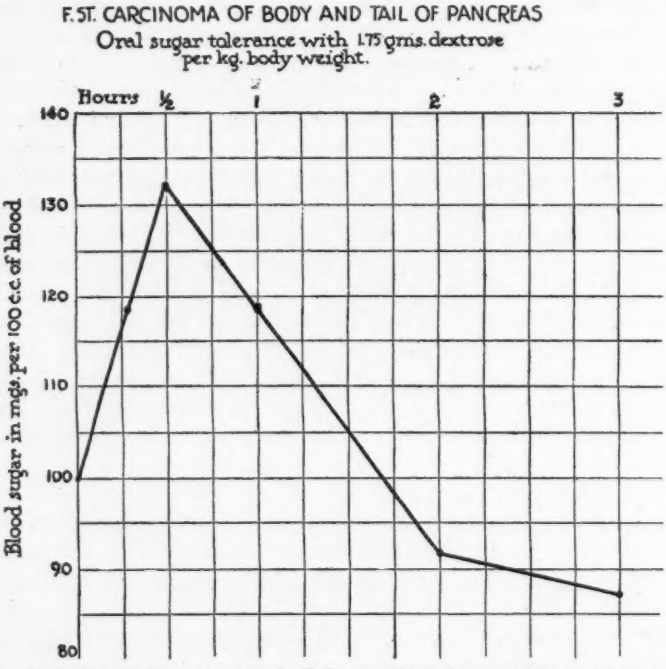


Fig. 2—Oral sugar tolerance curve in F. St., age 58, male case of Dr. S. W. McArthur of St. Luke's Hospital, Chicago. Patient's entire pancreas was transformed into the carcinomatous mass, with the exception of a small segment in the head of the pancreas.

a diet of carbohydrate 76 gm., protein 50 gm., and fat 150 gm., for the preceding two years.

The operation performed on January 21, 1929, has been described in detail elsewhere. A small hypoplastic pancreatic tail was divided with a high frequency cautery. He made a stormy convalescence, during which time drainage had to be instituted twice. He was discharged March 16, 1929, on the original diet taken before the operation, with 45 units of insulin. From March to May the insulin requirement remained steadily between 40 and 38 units. From April 26 on, insulin reactions began to

occur after the morning dose, which prompted a gradual reduction. On May 9, 110 days after the operation, the lowest level of 25 units was reached. From then on again the insulin had to be increased to 39-35 units, a stitch abscess of the abdominal incision having developed. On the week of June 4 the patient's diet was increased, as he still weighed only

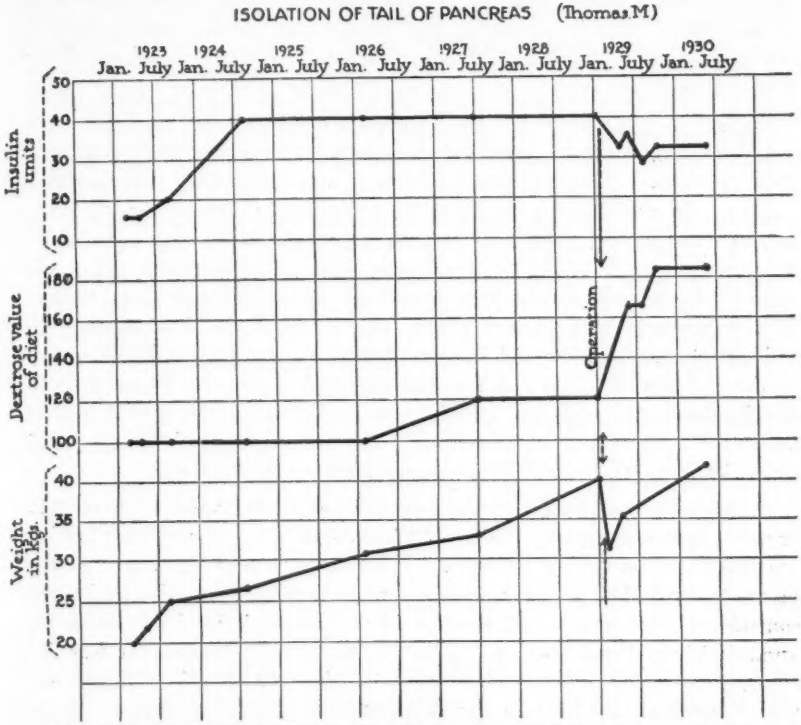


Fig. 3—Composite graph, showing the dextrose value of diet, insulin requirement and weight curve of Thomas M. The operation was performed on January 21, 1929.

80 pounds, as compared to 87 pounds before the operation. The new diet consisted of carbohydrate 102 gm., protein 75 gm., and fat 161 gm., a dextrose value of 166. On June 18, 1929, the insulin requirement was 39 units; on August 2, 29 units on the new diet. On May 31, 1930, seventeen months after the operation, the patient weighed 92 pounds (+5 pounds*), was 57½ inches tall (+1½ inches) and takes a diet of carbohydrate 118, protein 85, fat 160, dextrose value of 183 (+63) with 32 units of insulin (—8).

A severe diabetic child, whose previous history is well known, who has had diabetes of increasing severity for six years, was finally stabilized for two years on G. value 120, insulin 40. A year and a half after the opera-

*Figures in brackets indicate comparative data referring to the preoperative status. According to the latest report, patient's diet has been increased to a dextrose value of 200, without any increase in insulin.

tion the patient is growing and graining weight normally. While his insulin requirement is but slightly diminished, he is able to utilize an additional 80 grams of dextrose or its equivalent daily. Notwithstanding the small size of the isolated portion of the gland and despite serious postoperative reactions, the patient's diabetes has not become any worse and there is a moderate increase in carbohydrate utilization. This definite increase has occurred in a patient, who for six years had gradually lost tolerance, and who for the last two years before the operation had not shown any change at all.

Case No. 2. Eugene G., age 16, patient of Dr. Russell M. Wilder. A detailed history will be published elsewhere. The family history is negative for diabetes. He had measles, mumps, whooping cough and tonsillitis prior to six years of age and tonsillectomy at the age of six. He was treated for tuberculosis of the cervical lymph glands for three years and three months at the Sunnyside Sanitarium, being discharged as well at the age of ten. Since then he felt well until the age of 14, when it was noticed by the parents that he passed a great deal of urine and lost weight. He suddenly became drowsy and five days later was admitted in diabetic coma to the Billings Hospital, with a fasting blood sugar of 250 mgm., CO_2 39-35 volume per cent and a white count of 22,600. On insulin-glucose treatment he promptly recovered and was discharged in November, 1927, on a diet of C 90, P 65, F 216, calories 2600, without insulin.

The basal metabolic rate was —18 per cent. The weight was 33 kilograms. Between this date and July 27, 1929, the patient had nine further admissions to the Billings Hospital. While he remained sugar free at first he gradually had to be given more and more insulin, but could not be well controlled. On June 4, 1928, while in the hospital, he developed acute appendicitis and was operated on by Dr. George M. Curtis. He was discharged twenty days later on a diet of C 100, P 75, F 225, 2725 calories, with 17 units of insulin before breakfast and 12 units before supper. Later he has had several upper respiratory infections, which always affected his tolerance. He had been careless about his diet, reduced his insulin several times, ignored his diet and was admitted with ketonuria twice. Finally, on his tenth admission, as he had done so poorly on a low carbohydrate, high fat diet, and continued to pass sugar on a diet of C 120, P 85, F 200, with 80 units of insulin, it was considered advisable to try him on a high carbohydrate, low fat intake. The carbohydrate was increased to 200 grams, the fat dropped to 100. The urine became sugar free and it was necessary to cut the insulin dosage to 40 units. The carbohydrate was then increased to 300 grams without increasing the insulin. When discharged, August 30, 1929, his diet consisted of C 300, P 75, F 100, G. value of 354, 2400 calories, with 45 units of insulin.

On October 1, 1929, the patient was admitted to Wesley Memorial Hospital, under the diabetic management of Dr. William H. Holmes (Case No. 147,279). While preoperative studies were made, he developed an

acute upper respiratory infection with a temperature of 103 degrees, which, however, quickly subsided. He was operated on October 18, 1929, with a preoperative diet of C 300, P 75, F 100, and insulin units 35-35-35.

Under nitrous oxide and local anesthesia the tail of the pancreas was exposed and a strip of fascia lata tied snugly around it. The operation will be described elsewhere in detail. The abdomen was closed without drainage and the patient made an uneventful recovery. He left the hospital in fourteen days.

On November 7, 1929, the patient on the same diet was taking 60 units of insulin. His weight was 42.3 kilograms, the beight 159.9 cms. On November 18, he had abdominal cramps without rigidity. The leucocyte count was 9000; the urine was sugar free.

On December 17, on the same diet and 60 units of insulin, the patient weighed 46.7 kilograms. He received occupation in the hospital and from that time on received all his meals from the diet kitchen. On February 10, the insulin had to be reduced to 40 units a day, as he was getting severe insulin reactions. On February 25, he was readmitted to Billings Hospital because of an upper respiratory infection with a temperature of 101.1 degrees F. On February 27 he required 70 units of insulin, but March 3 it dropped to 35 units. During the following days the daily insulin varied between 45 and 50 units.

March 9, 1930, the diet was changed to C 69, P 50, F 215, with a G. value of 120. The insulin requirement fell to 18 units. This was its lowest point. The next week the insulin requirement started to rise and on March 23 chickenpox with an extensive eruption and fever was diagnosed. The insulin requirement rose to 50 units. On May 3, 1930, 100 grams of carbohydrate, 60 grams of protein, 206 grams of fat were allowed, which required 60 units of insulin. On May 20 he was persistently sugar free on this diet and insulin dosage. The body weight was 43.1 kilograms, the height 161 centimeters. On May 31, 1930, seven months after the operation, the patient weighed 43.1 kilograms (—0.6 kilograms), his height was 161 centimeters (+1.5 cms.). He was taking C 100 (—200), P 60 (—15) and F 206 (+106) with insulin 60 (—20).* According to Dr. Wilder's comment on his present condition, there was evidence of improvement in his tolerance up to the chickenpox infection, after which, however, the tolerance grew worse and is now but little better, if any, than before the operation. It might be that the stimulating (high carbohydrate) diet, taken before and several months after the operation, was injurious to the islets undergoing hypertrophy, and it is for this reason that the patient was put back on a low carbohydrate, high fat diet.

A diabetic child, whose disease is known to have been present for at least two years, and whose tolerance was rapidly growing worse, was operated on in October, 1929. Ligation of the tail of the pancreas was performed, the child making a rapid, smooth convalescence. Four months

*Since this article went to press, there has been a slow improvement in tolerance. The dextrose value is now up to 203; the insulin requirement could be diminished to 55 units.

after the operation, a reduction in insulin requirement took place. Five months after the operation, the high carbohydrate, low fat diet was changed to a low carbohydrate, high fat diet, with a corresponding large reduction in insulin. A little later a severe chickenpox infection aggravated the sugar tolerance. At present, seven months after the operation, and two months after the recovery from chickenpox, the tolerance, which had temporarily increased after the operation, is about the same as before.

In evaluating the result in these cases the following factors have to be considered:

Only years of close study will determine the end result. It seems, however, that in the first child, since whose operation more than a year

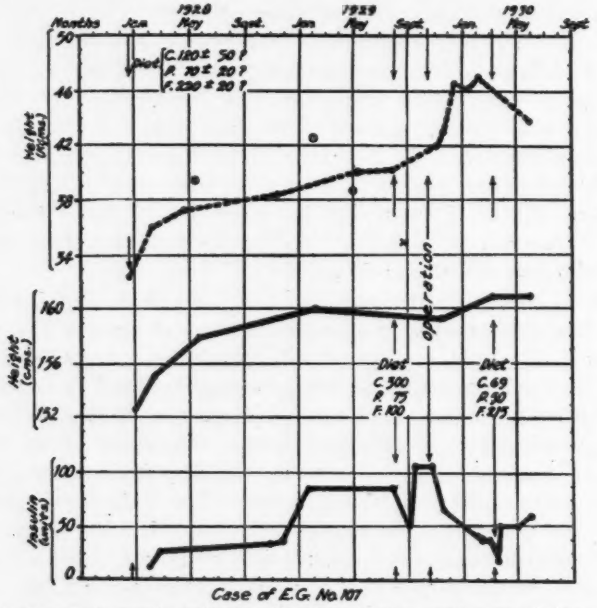


Fig. 4—Composite graph, indicating the diet, insulin requirement, height and weight curve of Eugene G. The operation was performed on October 18, 1929, during the Chicago meeting of the American College of Surgeons.

and a half have elapsed, is fairly stable now with 80 grams of additional dextrose and a little less insulin than before. When one considers that the tail end of the pancreas was abnormally short and that the postoperative convalescence was very stormy, even this modest improvement must be accepted as significant. In the second child, who had a large splenic pancreas, and in whom the modified operation (ligation instead of isolation) insured a far smoother convalescence, more marked results should have been observed. A fall in insulin requirement did take place, but the patient has up to the present time not recovered from the loss of tolerance which the chickenpox infection brought out. In a personal communication Dr. Russell M. Wilder has also pointed out that the high carbohydrate

diet, which had been given according to Porges and others to stimulate insulin production, might have been injurious and that better results could have been expected if the pancreas had been rested rather than stimulated in the period when the islets were undergoing hypertrophy. Sufficient time has not elapsed to permit a prediction as to the ultimate result in this case.

The parallelism between our animal experiments and the observations in the two clinical cases is striking. The change in tolerance is gradual, occurs around the fourth month and does not persist at its highest level but gradually returns to slightly above the preoperative level. The assumption that an islet hypertrophy takes place in the diabetic child could not be verified histologically, but seems very probably as spontaneous islet regeneration in diabetics has been described several times. It must be emphasized, however, that such an operation with resulting superregeneration of islets, does not hit at the real cause of diabetes, and that unless we shall succeed in protecting these new islets from injurious effects of nervous or hormonal origin, the new islets will not function any more efficiently than the original cells.

SUMMARY

1. Animal experiments have shown that there is a marked regenerative power of the insular apparatus of the pancreas. The islets undergo hypertrophy and hyperplasia, if parts of the gland are destroyed. Corresponding to the animal experiment, two diabetic children operated on showed a marked increase in tolerance, its maximum appearing around the fourth month.

2. For reasons that receive detailed discussion elsewhere, and are still being investigated, this improvement does not persist in its entirety, but a gradual decrease in tolerance occurs.

3. The future problem in attacking diabetes surgically lies not only in producing a hypertrophy of islets, but in protecting these islets from the continuous functional strain.

I wish to express my deep gratitude to Dr. A. C. Ivy, whose helpful suggestions have greatly aided my work and in whose laboratory the experiments have been conducted and are continuing. The operations were performed at Wesley Memorial Hospital. The diabetic management of the first case was in the hands of Dr. Charles A. Elliott, the second case was supervised by Dr. William H. Holmes.

BIBLIOGRAPHY

1. Jorns, G.: Experimentelle and klinische Beiträge zur Pathologie der Langerhans'slen Inseln des Pankreas. Beitr z. klin. Chir. **146**: 1. 1929.
2. Schmieden, V., and W. Sebening: Chirurgie des Pankreas. Arch. f. klin. Chir. **148**: 319. 1927.
3. Sprengell, H.: Klinische und anatomische Untersuchungen an ausgeheilten Pankreasfettnekrosen. Beitr. f. klin. Chir. **140**: 117. 1927.
4. Knopflach, J.: Pankreasatrophie und Lipomatose. Arch. f. path. Anat. und physiol. **261**: 666. 1926.
5. Baló, J. and H. C. Ballon: Effects of retention of pancreatic secretion. Surg. Gynec. Obst. **98**: 1. 1929.
6. Cit. by Gross, O. and N. Guleke: Die Erkrankungen des Pankreas. Berlin, Gustav Sprenger, 1924.
7. de Takáts, Géza: Correlations of external and internal pancreatic secretion. I. General considerations and review of literature. Arch. Surg. **19**: 771. 1929.
8. de Takáts, Géza: Correlations of external and internal pancreatic secretion. II. The histologic changes in the isolated tail of the pancreas. Arch. Surg. **19**: 775. 1929.

9. de Takáts, Géza, and I. T. Nathanson: Correlation of external and internal pancreatic secretion. III. The effect of ligation of the tail of the pancreas on blood diastase. Arch. Surg. **19**: 788. 1929.
10. de Takáts, Géza, Frances Hannett, Dorothy Henderson and I. J. Seitz: The effect of isolation of the tail of the pancreas on carbohydrate metabolism. Arch. Surg. **20**: 866. 1930.
11. Allan, F. M. and R. M. Wilder: Causes of failure in the treatment of diabetes of children. J. A. M. A. **94**: 147. 1930.
12. de Takáts, Géza and R. M. Wilder: Isolation of the tail of the pancreas in a diabetic child. J. A. M. A. **93**: 606. 1929.

THE PRACTICABILITY OF OVARIAN (AUTO-, HOMO- AND HETERO-) TRANSPLANTATION (WITH HISTOLOGIC PROOF)*

MAX THOREK, M.D.
Surgeon-in-Chief, The American Hospital,
CHICAGO

Since Knauer (1), in 1895, first successfully transplanted free ovaries from one site to another in the same animal, it has been abundantly proved by many other investigators, both experimentally and clinically, that ovarian transplantation, either as autografts or homografts, and to a more limited extent heterografts, is a practical surgical procedure. It has definite indications and when executed with proper technic it will in many instances give the desired results.

EXPERIMENTAL OVARIAN IMPLANTS IN ANIMALS

1. *Autografts:* Knauer's successful experimental autografts were followed by many others, including those of Grigorieff (2), Uffreduzzi (3), and Benesch and Kohler (4). Long and Evans (5) made nineteen autotransplantations in rats, placing the implant in the mesometrium, omentum, spleen, etc. In fourteen of these the implant survived and functioned. Similar work has been done by many others. Some of the investigators found that the implantation of free ovaries in the uterine cavity was followed by pregnancy.

2. *Homografts:* Early work by Foa (6) and others showed that homotransplantation of ovaries could be successful, although not to the same degree as autografts. Pettinari (7), especially, showed that such implants would live, elaborate the normal internal secretion of the ovary and assume the germinal function. The literature showed quite clearly that pregnancy sometimes followed ovarian homotransplantation in spayed animals.

Opinions have varied considerably in regard to the functional results obtained from ovarian homografts as compared with autografts. Sand, Marshall, Athias, Pettinari, Lipschütz and others have found that with proper technic homografts were successful. Sand (8) performed twenty-four homotransplantations in rats. Four months later thirteen of these transplants were found to be functioning. He also performed twenty-nine ovarian homotransplantations in castrated male rats and in thirteen of these the transplant could be determined several months later. On the other hand, in fifty-two similar transplants in male castrated guinea pigs, there was only one feminization in the Steinach sense. As will be shown later, the site of the transplant and the technic of implantation have everything to do with the survival and function of the transplant.

*Read before the Fourteenth Annual Meeting of the Association for the Study of Internal Secretions, Detroit, Michigan, June 23, 1930.

Tamura (9) (employing a special technic to be described later) in thirty-one experimental ovarian transplants from young female to adult male castrated mice, considered the result a success regarding the taking of the transplant, and found that when investigated at periods varying from ten to thirty-five days following implantation the transplants retained their typical ovarian structure, and that the germinal epithelium remained intact.

3. *Heterografts:* As a general rule, attempts at heterotransplantation of ovaries in animals have been failures. Lipschütz (10) believes that this is due to the difference in biologic relationship. After several years' experimental work in grafting ovaries from rabbits into the kidneys of guinea pigs, Lipschütz stated that he never had observed any endocrine effect from such transplants, nor a durable survival. I shall, however, have more to say on this point presently and hope to show that the possibility of successful ovarian heterotransplantation depends upon the closeness of the blood affinity between the donor and the recipient of the transplant.

The general conclusions to be drawn from the literature on experimental ovarian transplantation in animals are that autotransplants commonly survive and show secretional activity; that homotransplants are less successful, the success being in general a matter of technic; that heterotransplants commonly fail, both in regard to survival and function.

OVARIAN TRANSPLANTATIONS IN THE HUMAN SUBJECT

Morris (11), in 1895, was the first, after radical removal of the ovaries and tubes in a young woman, to transplant a piece of ovary to the stump of one tube. This woman became pregnant a month later. Such autotransplantation has been repeated by a number of investigators, commonly with success, but the technic of autoplastic free ovarian transplants has varied. A number of successful results have been reported following human ovarian homotransplantation.

In 1928 the author reported (12) upon forty-four personal cases of human ovarian homotransplantation. Thirty-six of these patients were traced and about 60 per cent of those who had suffered from exaggerated psychic and neurotic symptoms were completely restored to health. The other cases were ameliorated more or less. In five of these patients who were subsequently operated upon for abdominal condition there was an opportunity to examine the transplant one to four years after its implantation. In four instances it was found *in situ,* diminished in size but apparently surviving and well vascularized. No histologic examination was possible. My opinion, based on personal experience, is that ovarian homotransplantation is a practical surgical procedure which has definite indications, with a fairly well established degree of durability of results.

Among the clinical manifestations that may reasonably be ascribed to hypofunction of the ovary, Novak enumerates the following:

"1. Amenorrhea (absence of menstruation), hypomenorrhea (scanty menstruation), and oligomenorrhea (abnormally infrequent menstruation), delayed puberty and premature menopause.

"2. The vasomotor symptoms of the menopause (either natural or artificial).

"3. Some cases of sterility (probably only a small proportion).

"4. Possibly some cases of so-called primary dysmenorrhea, genital hypoplasia, obesity, repeated abortion, and menstrual headaches."

According to Hirst, sexual frigidity belongs in this group.

Norris and Behney (12a) recently have reported on thirty-one autotransplantations. They found that the majority of such implants "take" but that they probably do not survive more than two or three years. They believe that menopause phenomena when they occur approximate normal, even long after the transplant has disappeared.

Martin (13), in 1922, reviewed the literature of the subject and reached the general conclusion that while autotransplants gave some evidence of success in deferring the symptoms of the menopause and delaying the cessation of menstruation, homotransplants and heterotransplants gave practically no such evidence. I think that since the expression of this opinion much has been accomplished which would cause a modification of it. As a matter of fact, there are several circumstances apart from the nature of the transplant itself which are concerned with a successful outcome.

FACTORS CONDUCIVE TO SUCCESSFUL OVARIAN TRANSPLANTATION

I will assume that it is already proved that free ovarian tissue, no matter where implanted, if it survives and becomes vascularized, will continue to discharge its hormones and that these hormones will affect the organism about the same as that of the normal ovary in its proper situation. These remarks, of course, refer specifically to free ovarian transplants. They do not refer to pedicled transplants and the functional results are also modified by the presence or absence of the uterus or ovaries, or both, in the recipient of the transplant. Biedl (14) believed that a portion of one ovary in any part of the body sufficed for this function.

There are, however, many other factors which enter into successful implantation. These are: (a) The site of the implantation; (b) the technic followed; (c) the age of the implant; (d) the condition of the implant at the time of operation; (e) the blood affinity between the donor and the recipient. All these factors must be taken into consideration in connection with the fundamental conditions upon which survival of the implant and its functional activity depend—that is, its successful vascularization and the degree of activity of its germinal epithelium. If the transplantation is to be successful, proliferation of the germinal epithelium must begin soon after vascularization is definitely established. Keeping these matters in mind, let us consider the factors enumerated.

Site of Implantation: While, other things being equal, an ovarian transplant will "take" in many situations there are certain preferential sites. As early as 1907 Marshall and Jolly (15) described experiments in

which they transplanted ovaries into the kidneys of rats. The kidney was split, the transplant inserted and the kidney reclosed. This site was selected because of the rich vascularization. Lipschütz reports that since 1923 he has been transplanting ovaries into the kidneys of rabbits and guinea pigs, with definitely good results. He also has made a series of experimental homotransplantations, following the technic of Marshall and Jolly. In seventy-four such transplantations in guinea pigs sixty-four gave positive results. That is to say, 85 per cent of these intrarenal homotransplants proved successful.

In my extensive work on testicular transplantation, I decided that as an alternative to supraperitoneal transplantation the retrorenal space, between Gerota's capsule and the endo-abdominal fascia, should be very suitable for such transplantations and an improvement in the technic. After much experimenting this was found to be the case and a technic for this transplantation site was evolved and described in my book on "The Human Testis" (15a), where it is fully illustrated. The vascular supply to this space is through the lumbar vessels. The transplant is deposited in this space without suturing. I have used this site in many of my clinical cases and experimental studies of ovarian homotransplants (Fig. 1). The

Fig. 1. Human ovary, transplanted perirenally (author's method) into Macacus rhesus. Refrigerated forty-eight hours.

next best sites for implantations in clinical cases are the cervical and the supraperitoneal regions.

Tamura (9), reporting upon experimental ovarian homotransplantations in mice, recently has described a method of implanting the ovarian transplant on the surface of the kidney. His incision is made just posterior to the last rib, exposing the capsula adiposa and the kidney. The kidney is detached from the abdominal wall and the tunica fibrosa is incised and folded back. The implant is placed in the wound, the lips of the tunica fibrosa are pulled together as far as possible, the capsula adiposa replaced and the abdominal muscles and skin closed.

This technic differs from that of Marshall and Jolly and of Lipschütz only in so far that in the latter the kidney proper is split. It is only a

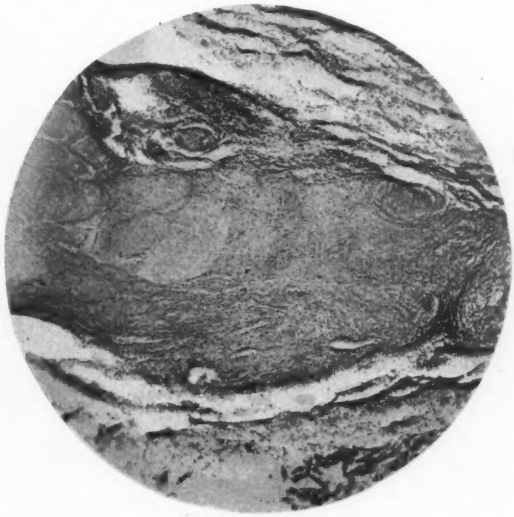


Fig. 2. Human ovary, twenty-four hours refrigeration, two months after implantation. X40.

variant of my original perirenal transplantation, and although it may be allowable for experimental animal purposes, as in the work of the investigators cited, it would be unsurgical for clinical purposes. My perirenal transplantation is thoroughly effective from the standpoint of vascularization; it is practical, simple, and offers no danger to the patient.

Technic: Ovarian transplantation should be executed under strict asepsis and with all surgical precautions necessary in any major surgical operation. This applies to both donor and recipient and it is best, if possible, to operate simultaneously on the donor and the recipient. Some, Steinach for instance, have expressed the opinion that some time should elapse between the removal of the ovary and its implantation. Lipschütz (10), however, maintains that intrarenal transplants have, in his hands, given just as good results when implanted immediately after castration as

when a certain time had elapsed. Ovarian tissue may, however, be preserved for some time in a refrigerator. Zondek and Wolff (17) kept human ovarian tissue at a temperature varying from zero to —12° C. and after five days transplanted it into an amenorrheic patient who, two months later, menstruated. The researches of Lipschütz (16), nevertheless, leave no doubt that ovarian tissue dies at a temperature below zero. Other authors have found that freezing the implant injures it and that if such material is transplanted it fails in its endocrine function. Lipschütz,

Fig. 3. Position of human ovary refrigerated ninety-six hours and transplanted suprapertioneally into Macacus rhesus. Three months after transplantation.

however, found that ovaries preserved in ice did function. In twelve intrarenal transplantations in which material which had been kept in ice for from one to three days was used, six positive results followed in animal transplantations. The proportion of successes diminished the longer the ovary was kept at low temperature before being transplanted.

In my refrigeration experiments extending over a period of a year I have found that good results have been obtained only when the time of refrigeration of the transplant, human or ape, did not exceed ninety-six

hours. If a transplant preserved for a longer time than this was used failure resulted. Lipschütz considers that a transplant kept at a temperature of from 1° to 3° C. will preserve its vitality up to sixteen days, and that if transplanted it will survive and function endocrinologically (Figs. 2-3).

Site and Condition of the Implant: For good functional results it has generally been considered that the transplant should be removed from a young donor, although Lipschütz and Tamura both report good results

Fig. 4. Human ovary transplanted into Macacus rhesus (neck). Refrigerated twenty-four hours. Eleven months after implantation. Van Gieson stain.

from the transplantation of adult ovaries. A whole or half of an ovary may be used.

It goes without saying that the ovarian tissue to be transplanted must be in a healthy and functioning condition, but an ovary whose function in the donor may have been deficient or failed because of some systemic condition may function satisfactorily in its new location in the recipient. Furthermore, an infantile ovary may give normal function when transplanted. Lipschütz showed that in guinea pigs an immature ovary

functioned endocrinologically when transplanted into castrated adult animals, but if transplanted into immature castrated animals the endocrine effects are not apparent until the animal arrives at the age of puberty.

When an ovary is transplanted into a castrated male guinea pig the Graafian follicle shows a tendency to enlarge but a corpus luteum is never found. On the other hand, in a castrated female such a transplant almost always shows a corpus luteum. It has been observed that in a normal

Fig. 5. Human ovary transplanted into Macacus rhesus (neck). Refrigerated twenty-four hours. Eleven months after implantation. Van Gieson stain. Atretic follicles.

woman with both ovaries functioning *in situ*, if a third ovary is implanted and "takes" no corpus luteum is ever found in it; but in the majority of castrated women in whom a transplantation is carried out, corpora lutea can be demonstrated in the implant.

Blood Affinity: The success of organ and tissue transplantation in general varies directly according to the difference in blood affinity between the donor and recipient. Moorehead (18) recently referred to experiments by Staige Davis showing the possibility of *matching or typing tissues for implantations the same as the typing of blood. Such implants*

Davis terms "isografts." In sex gland transplantations the degree of blood relationship between the donor and recipient is a matter of prime importance. In my book already cited I pointed out (Chapter xiii, pp. 327, et seq.) the value of Nuttal's verification of the affinity of human and certain anthropoid bloods, the highest type of affinity being between the bloods of Cercopithecidea and Simiidea. This close affinity which seems to substantiate Darwin's conception, so far as tissue relationship is concerned, was advanced as a reason for the success of testicular transplantations between man and the higher anthropoids, and vice versa.

These remarks apply also to ovarian transplantations. Furthermore, it may be said that even in homotransplants the matching of the blood of the donor and the recipient is important. Both should be of the same blood group to insure the best results.

3. *Heterografts:* The literature contains only a few reports regarding ovarian heterotransplantation in the human female.

The above remarks regarding technic, blood affinity, and so forth have particular reference to heterotransplants and naturally lead to my own work on ovarian heterotransplantations, which I desire to report in this paper.

AUTHOR'S PERSONAL WORK ON OVARIAN HETEROTRANSPLANTS

Apart from clinical ovarian homotransplants, I have during the past three years conducted a series of experiments having for their object the possibility of an interchange by transplantation between various glands in mammals, including the human species.

One set of these experiments dealt with the transplantation of human ovary tissue into Macacus rhesus monkeys. I submit herewith the histologic proof of the successful result of an ovarian implant from the human to Macacus rhesus, observed for eleven months after its implantation. This is, so far as I know, the first complete proof of such a successful heterotransplantation from human to Macacus rhesus. The histologic illustrations (Figs. 4-10) show all the elements of the transplanted ovary preserved for eleven months, with the exception of primordial ova.

Lipschütz states that Voronoff speaks in the lay press of the implantation of a human ovary into a castrated Macacus rhesus, following which the animal menstruated. No histologic proof is offered as to the condition of the implant, nor is a report made in any scientific publication.

Commenting upon this experiment Lipschütz remarks that, if ethically permissible and if human material is available, this experiment should be repeated, but that results will only be impressive if two fundamental conditions are fulfilled, namely, (1) that the suspended genital functioning of the host (all the sexual cycle phenomena in the ape) is resumed; and (2) that the microscope must without any doubt show the surviving transplanted ovary with exclusion of the possibility of any small portion of the true ovary remaining behind. The practical importance of the whole question is so great that the experimental proofs should permit of no equivo-

cation, and I submit that the proofs I offer here are of this nature. I have not been able to find any other histologic proof of this or any similar experiment in the literature and, therefore, claim priority in this regard.

In a castrated sexually mature (menstruating) Macacus rhesus following cessation of menstruation a human ovary was transplanted into the neck (perithyroid region). Eleven months later the implant was removed and the conditions illustrated were found. While regular menstruation

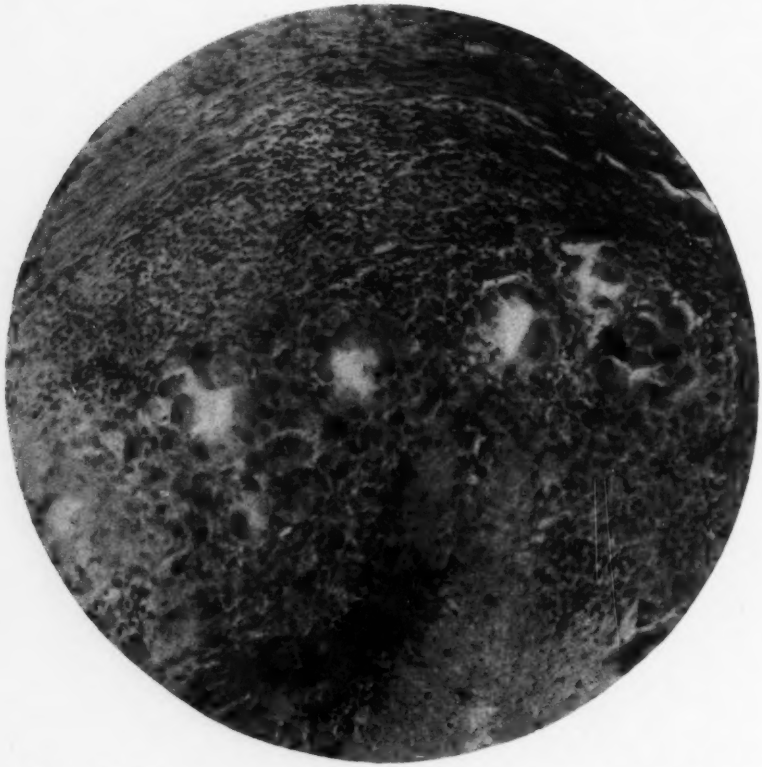


Fig. 6. Human ovary transplanted into Macacus rhesus (neck). Refrigerated twenty-four hours. Eleven months after implantation. Van Gieson stain. Atretic follicles. Invasion of small theca cells.

did not reappear after implantation, vaginal smears and congestive phenomena about the genitalia attest the endocrine function of the implant.

Histologic Findings: Tissue embedded in paraffin. Sections cut 8-10 microns, stained with hematoxylin-eosin and with Van Gieson's method.

Under low power magnification the tissue is found to be subdivided by strands of connective tissue into round areas. Near the periphery the connective tissue is condensed into a fibrous mass. The areas encircled present different aspects; in some of these the center of the area is formed

by large cells with a pale or oval large nucleus and with well defined nucleolus. The cytoplasm shows in places polygonal outlines; in other places the cells seem to be confluent into large giant cells, with accumulations of many nuclei. At the periphery of these areas large cells, as described above, are arranged in a palisade-like manner. Peripherally from these there are many layers of elongated cells with dark staining

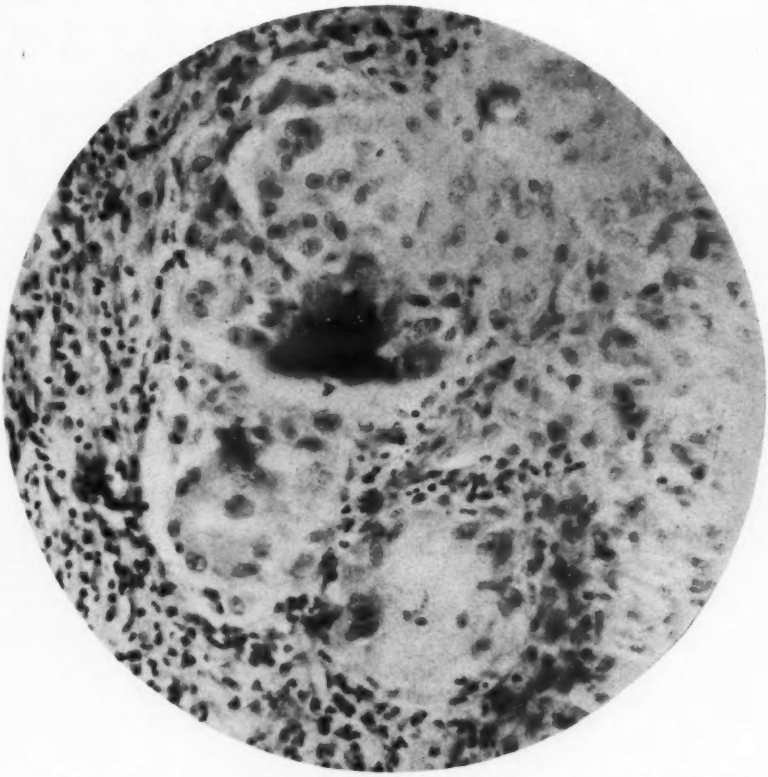


Fig. 7. Human ovary transplanted into Macacus rhesus (neck). Refrigerated twenty-four hours. Eleven months after implantation. Van Gieson stain. Giant cell formation.

nuclei, embedded in a fine network of connective tissue fibers. A third group is made up of large areas which are completely filled with cellular masses. Two types of nuclei may be distinguished: (a) dark staining round or irregular ones and (b) round, pale nuclei with well defined nucleolus.

Goldzieher and Sherman (24) have studied the formation of hyaline in sixty ovaries. Five types of hyaline bodies were described. They derive from lutein bodies, from atretic follicles, from lipoidal cells of the ovarian stroma, from ordinary stroma cells and from blood vessels, respectively. The histogenesis of a hyaline body can be distinguished only

in the early stage of its formation. Combination forms are common.

The clinical significance of the ovarian hyalinization requires further comparative studies.

I wish to express my appreciation to Dr. M. A. Goldzieher for his kindness in examining the microscopic section described here. His findings were as follows:

"The section of the ovary, stained after van Gieson, reveals a lobular structure as the result of hyalinized connective tissue septa, separating areas of different size and shape. This hyaline connective tissue is obviously the product of an ordinary process of scarring and the hyaline itself is derived from the collagenous fibrils which again are produced by fibroblasts.

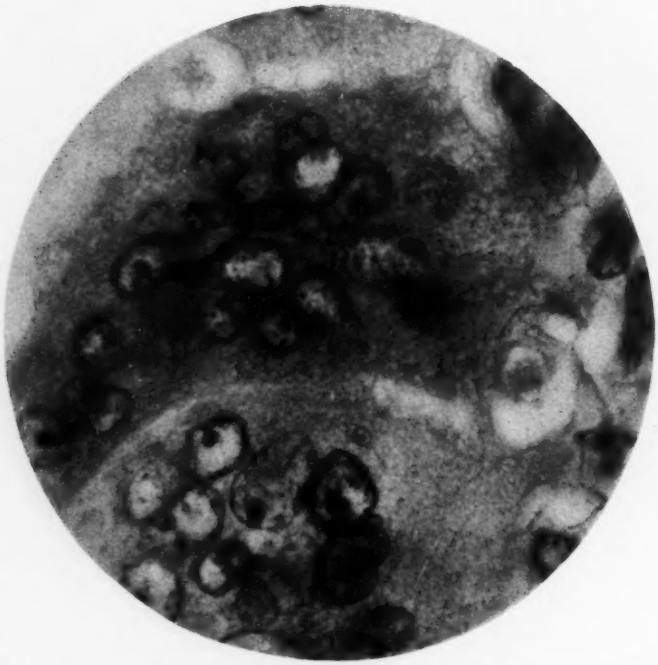


Fig. 8. Human ovary transplanted into Macacus rhesus (neck). Refrigerated twenty-four hours. Eleven months after implantation. Van Gieson stain. Follicular cells simulating multinuclear giant cells.

"Within the lobules, we find peculiar, large cells with a remarkable tendency of forming giant cells. They are surrounded by more or less massive granulation tissue and occasionally by groups of polynuclear leucocytes. These cells have a remarkable tendency of forming structures vaguely suggesting lutein bodies. These cell groups are oval or triangular and sometimes show a peculiar wavy character. The center of these structures contains what appears to be hyaline material, most of which, however, stains yellow while bright red hyaline is less conspicuous. It is my impres-

sion that the yellow material derives from a combination of necrobiosis, fibrinous exudation and compares well with the processes, which are met with in the involution stage of the lutein bodies.

"There are other hyalinized areas which stand out particularly well in some of the H and E sections. This extensive hyalinization is of a peculiar trabecular character. Between the hyaline trabecles cells are pres-

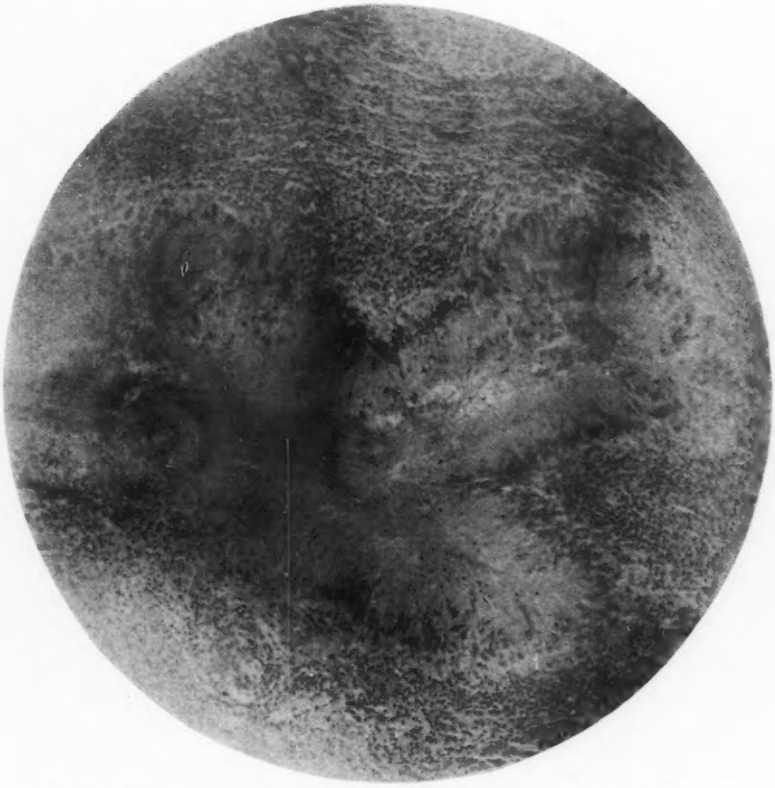


Fig. 9. Human ovary transplanted into Macacus rhesus (neck). Refrigerated twenty-four hours. Eleven months after implantation. Van Gieson stain. Corpus albicans (area of hyaline degeneration) or corpus luteum?

ent which are of the type of the ovarian interstitial cells, although their nuclei are sometimes somewhat larger, vascular and not very different from those seen in the large or giant cells described above. The similarity is enhanced occasionally by the identical behavior of the nuclei. Yet, as a whole, these cells are different and have no tendency to form giant cells.

"This type of hyalinization is morphologically identical with that observed in the ovarian stroma which I have described as independent from follicles or lutein structures.

"It is my impression that the large cells, including giant cells, derive from granulosa cells and the hyalin masses about which they often center are products of necrosis, exudation and perhaps secretion. The other type of hyalinization is definitely interstitial and indicates a similar metabolic disturbance of the interstitial cells to that which we find so frequently in ovaries removed with fibroids of the uterus.

"As a whole, the changes observed are, besides an inflammatory component, mostly of a regressive character. Yet, it seems that many of the specific cells of the ovary are in a state where they might be still capable of surviving and producing hormonic effects."

Fig. 10. Human ovary transplanted into Macacus rhesus (neck). Refrigerated twenty-four hours. Eleven months after implantation. Van Gieson stain. "Lutein cells" or lipoid containing cells in hyaline degenerated areas.

Comment: What has been described apparently represents different stages of follicular atresia and corpora lutea involution. Connective tissue invasion from the mesenchymal tissue of the neighborhood did not seem to have played an important rôle. The presence of corpus luteum cells persisted after eleven months with well defined cell characteristics and excellent stain affinities. Hyaline changes observed in the adult ovary were not found in the transplanted embryonic ovary (Figs. 11 and 12).

Knauer and Steinach (21) reported the survival of animal ovarian autotransplant for three and one-half years, respectively, and Mauclaire

(22) and Nattrass (23) saw such transplants living for eight and nine and one-half years after implantation in the human subject. In my clinical homotransplants as already stated, they were found to be functioning at periods varying from one to four years after implantation. Athias (24), in his animal ovarian homotransplants, found that follicles were histologically recognizable in the transplants two years after implantation.

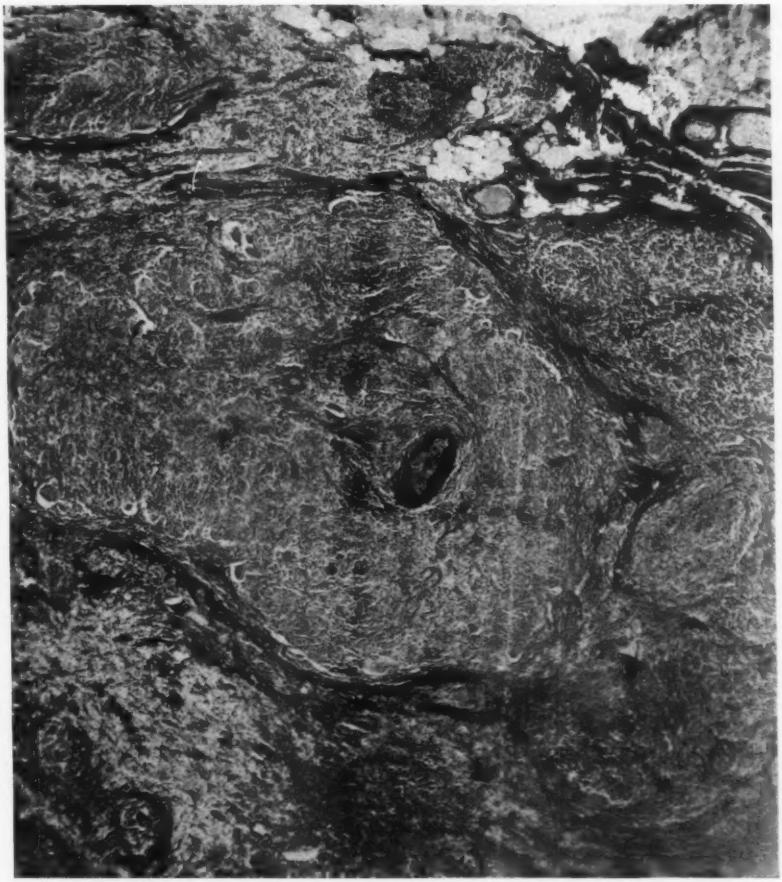


Fig. 11. Human fetal ovary transplanted into omentum of Macacus rhesus. Three months after implantation. Van Gieson stain.

Moore (25) found primary follicles in animal transplants 332 days after implantation, although the transplant was decreasing in size. In Lipschütz's experiments in guinea pigs he stated that 70 per cent of the cases in which the transplant "took" were functioning after nine months; that is to say, giving evidence of endocrine secretional activity and microscopic

evidence of follicular activity. In some cases more than a year and a half had elapsed.

There is, so far as I know, no case reported in the literature of an ovarian heterotransplant proved histologically to be functioning for a period even approximating eleven months after implantation.

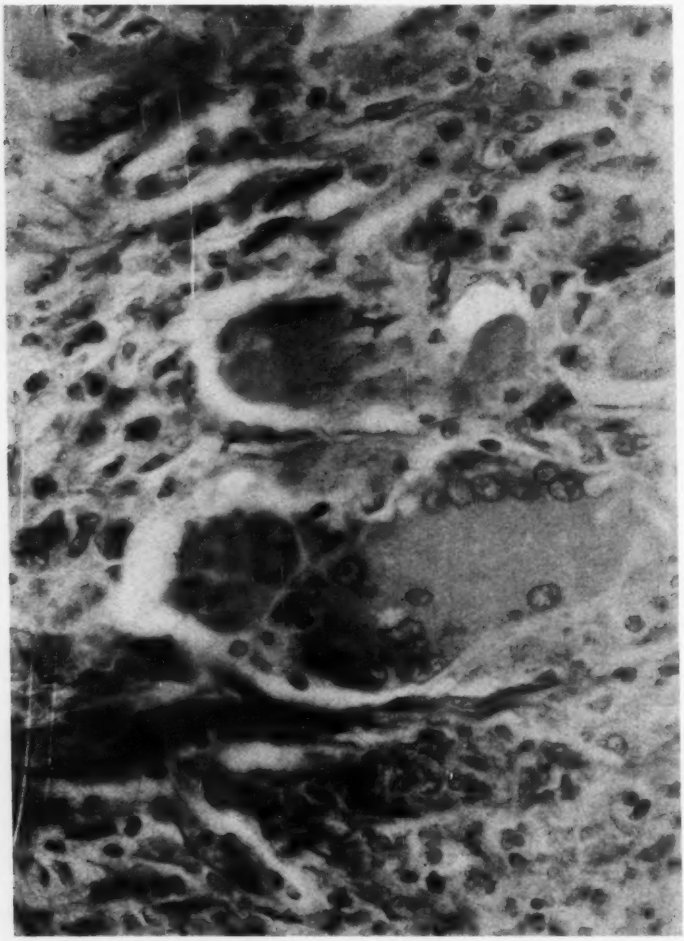


Fig. 12. Human fetal ovary transplanted into omentum of Macacus rhesus. Three months after implantation.

No claim is made that ovarian transplantation is of permanent value. The literature shows that after a time, perhaps a few years, the transplant will disappear, but while it survives it fulfills the functions, or at least some of them, of the endocrine secretion of the ovary. The indications for such a transplantation, whether as a prophylactic or therapeutic measure

in induced or natural menopause, are well known and I will not discuss them here. I will merely say that the proof of the possibility of successful ovarian transplantations has greatly widened the scope of practicability of this surgical procedure.

I will take the opportunity of repeating here what I have reiterated in the case of testicular transplantations, that such operations have no place as "rejuvenation" procedures, an aspect which has, unfortunately, been stressed in newspapers and to some extent in medical journals, to the detriment of surgical progress by affording opportunities to quacks and charlatans to delude and mulct the gullible public. There is no rejuvenation in the accepted sense possible by such operations, but successful testicular and ovarian transplantations do unquestionably improve the waning physical and psychic condition of patients and retard the onset of symptoms of senility. There is too much proof of this both in animals and the human subject to permit of the least doubt. From personal observation I believe the number of successes is greater in women undergoing implantation than in men.

BIBLIOGRAPHY

1. Knauer, E.: Centralbl. f. Gynaek. **20**: 524. 1896.
2. Grigorieff, W.: Centralbl. f. Gynaek. **21**: 663. 1927.
3. Uffreduzzi, O.: Ann. di ostet. **2**: 57. 1911.
4. Benesch, F. and R. Kohler: Zentralbl. f. Gynaek, **47**: 2513. 1924.
5. Long, J. A. and H. M. Evans: Cited by Lipschütz (10).
6. Foá, C.: Arch. ital. de biol. **35**: 364. 1901.
7. Pettinari, V.: "Greffe ovarienne et action endocrine de l'ovaire," Paris, 1928.
8. Sand, K.: Handb. d. norm. u. path. Physiol. **15**: 251. 1926.
9. Tamura, V.: Proc. Roy. Soc. Edinburgh, **47**: 148. 1926-1927.
10. Lipschütz, A.: "Die experimentellen Grundlagen der Eierstocksverplanzung," Budapest, 1930, and references therein.
11. Morris, R. T.: "Lectures on Appendicitis," New York, 1895, p. 156.
12. Thorek, M.: Illinois M. J. **54**: 389. 1928.

12a. Norris, C. C. and C. A. Behney: Surg. Gynec. Obst. **49**: 642. 1929.

13. Martin, F. H.: Surg. Gynec. Obst. **35**: 573. 1922.
14. Biedl, A.: "Innere Sekretione," 4 Aufl., 1922. Urban & Schwarzenberg, Berlin and Wien.
15. Marshall, F. H. A. and W. A. Jolly: Tr. Roy. Soc. Edinburgh, **45**: (Part 3) 589. 1907.

15a. Thorek, M.: The Human Testis. 1924. Philadelphia. Pp. 397 and 410.

16. Lipschütz, A.: Handb. d. biol. Arbeitsmethoden (Abderhalden), **5**: 357. 1926.
17. Zondek, B. and E. Wolff.: Zentralbl. f. Gynaek. **47**: 2195. 1924.
18. Moorehead, F. B.: Bull. Chicago Med. Soc., Dec. 11, 1929.
19. Steinach, E.: "Verjungung durch exper. Neubelebung, etc.," 1920.
20. Mauclaire, P.: Bull. Soc. Anat. de Paris, **92**: 167. 1922.
21. Nattrass, J.: Brit. M. J. **1**: 1051. 1923.
22. Athias, M.: Festsch. Ramon y Cajal, **2**: 79. 1922.
23. Moore, C. R.: J. Exper. Zool. **33**: 126. 1921.
24. Goldzieher, M. A. and I. Sherman: Arch. of Path. **5**: 906. 1929.

THE RELATION OF WEIGHT TO DIABETES*

HENRY J. JOHN, M.D.
Cleveland Clinic
CLEVELAND, OHIO

Overweight as a possible etiologic factor in diabetes has been discussed by many writers, and the present study of the weight in 528 cases was undertaken to ascertain whether or not diabetics as a rule are much overweight and the part that this condition may play in the production of the disease. The maximum weight of each patient was used in the preparation of the data presented in preference to the weight on admission, as it seemed probable that the former would serve better as an index to the rôle of overweight in the development of diabetes.

Overweight presupposes overeating, and overeating presupposes an increased demand on the insulogenic function of the pancreas, which, if it

TABLE I
NORMAL WEIGHT CHART

Age	Boys	Girls
1	21.0	21.0
2	27.0	27.0
3	32.0	32.0
4	36.0	36.0
5	41.0	41.0
6	46.0	44.4
7	50.7	49.4
8	55.4	53.5
9	64.0	59.7
10	67.1	66.1
11	75.9	75.2
12	81.3	80.7
13	92.6	97.3
14	103.6	105.6
Height	**Men**	**Women**
4′ 8″	...	112
4′ 9″	...	114
4′ 10″	...	116
4′ 11″	...	118
5′ 0″	126	120
5′ 1″	128	122
5′ 2″	130	124
5′ 3″	133	127
5′ 4″	136	131
5′ 5″	140	134
5′ 6″	144	138
5′ 7″	148	142
5′ 8″	154	146
5′ 9″	159	150
5′ 10″	165	154
5′ 11″	170	157
6′ 0″	176	161
6′ 1″	181	...
6′ 2″	187	...
6′ 3″	192	...
6′ 4″	198	...
6′ 5″	203	...

is in any way subnormal, could easily be exhausted to the point of insufficiency, with the appearance of diabetes. While this reasoning is merely

*Read before the Fourteenth Annual Meeting of the Association for the Study of Internal Secretions, Detroit, Michigan, June 23, 1930.

clinical, without sufficient scientific evidence to substantiate the hypothesis, it offers a working basis of value to the clinician and the student in an effort to understand the evolution of diabetes. In time the further information needed may be made available, and data may be secured on the functional capacity of the pancreas before the development of diabetes and its relation to this condition. This is the goal at which we are aiming, but much more time will be required to accumulate and digest the facts.

In this study the cases of diabetes have been classified as follows: (1) by the decade in which symptoms developed, (2) by the percentage of

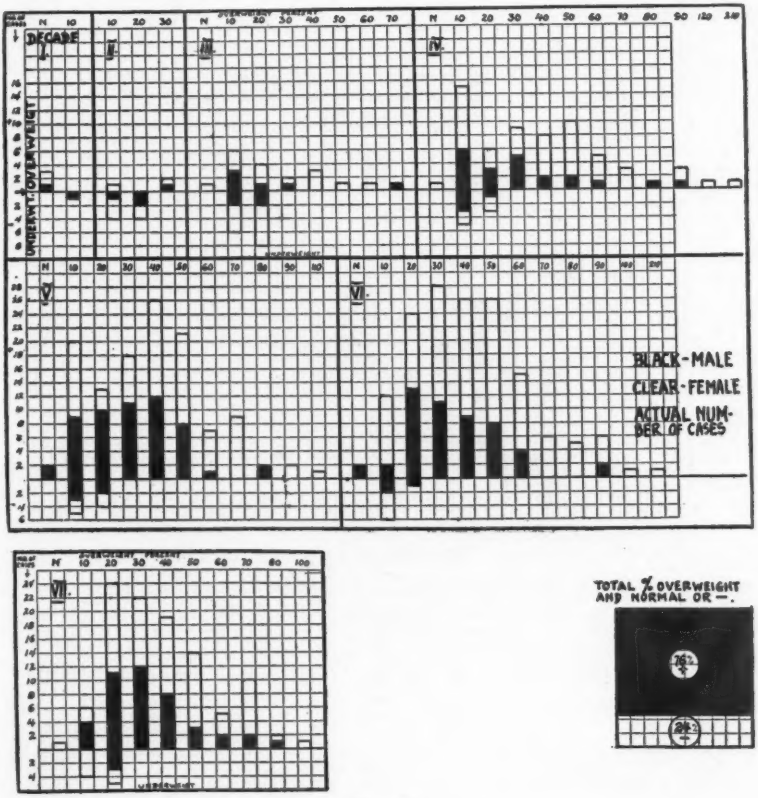


Chart 1.

over- or under-weight, (3) by sex, and (4) in comparison with a large series of normals which were furnished by Dr. F. G. Brathwaite of the Equitable Life Assurance Society of New York City. The estimations in my cases are based on the normal standards in use at the Cleveland Clinic, which are shown in Table 1.

Chart 1 shows graphically the distribution of overweight by decades in males and females. The preponderance of overweight, increasing in each

succeeding decade, is striking. The scale in the lower right-hand corner illustrates the proportion of patients who were overweight to those who were normal or underweight, all who were not more than ten per cent above normal being included with the normal. It should be noted that in three-quarters of the cases the weight was excessive, while in one-quarter it was normal or below.

Apparently the sex was without great significance as there was little difference in the results according to this classification, 72 per cent of the males examined and 81 per cent of the females being overweight.

In Chart 2 the entire series of 528 cases is analyzed to determine the percentage of overweight in the group as a whole and the relative propor-

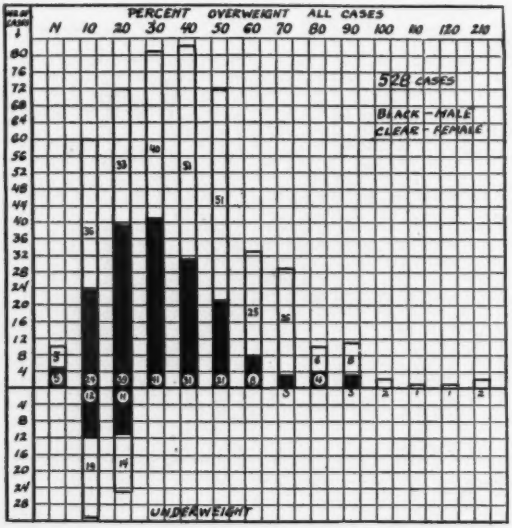


Chart 2.

tion of overweight in male and female. Again the marked preponderance of overweight is shown, running as high as 210 per cent.

In Chart 3 the entire group is analyzed by decades, regardless of sex. In the lower portion is shown the percentage in each decade of those who were underweight, normal, or not more than ten per cent above normal. In the upper portion is shown the percentage of those who were frankly overweight. Here the marked increase in overweight with each succeeding decade is graphically demonstrated, as well as the proportion between over- and under-weight.

These three charts depict the increase of weight with age in diabetic patients. In order to furnish a further basis of comparison, Dr. F. G. Brathwaite of the Equitable Life Assurance Society was requested to supply from his files the available data on the weight of non-diabetics.

Although this group does not afford a perfectly just parallel, since life-insurance statistics are based on a more or less picked class, yet it does provide a fairly satisfactory standard by which to estimate the extent of overweight in my series of diabetic cases.

In Table 2 is presented the exact information received from Dr. Brathwaite. Here only the averages in each group are shown, rather than a

TABLE II

INCREASE IN WEIGHT IN POUNDS FOR EACH FIVE-AGE GROUP. DATA FROM THE EQUITABLE LIFE ASSURANCE SOCIETY, 1930.

Age Group	Aggregate Weight	Average Weight	Increase or Decrease in Weight
	Men		
15–19	726170	138.9	.....
20–24	5082381	148.2	+9.3
25–29	7585199	152.6	+4.4
30–34	7254884	156.7	+4.1
35–39	5799329	160.1	+3.4
40–44	3883682	162.2	+2.1
45–49	2252252	164.4	+2.2
50–54	1225947	165.5	+1.1
55–59	596544	165.3	−0.2
60–64	189068	165.3	+0.0
65–84	43994	166.0	+0.7
	Women		
15–19	570188	124.1	.....
20–24	2837446	127.9	+3.8
25–29	4084088	130.5	+2.6
30–34	3784089	133.9	+3.4
35–39	2939572	137.4	+3.5
40–44	1886537	140.7	+3.3
45–49	1161774	143.1	+2.4
50–54	662704	145.0	+1.9
55–59	289318	145.0	+0.0
60–64	82878	143.9	−1.1
65–74	15476	138.2	−5.7

TABLE III

COMPARISON OF WEIGHT INCREASE (IN POUNDS) IN NORMAL AND DIABETIC SUBJECTS

Decade of Life	Equitable Life Normal Persons	Author Diabetic Patients
III	5.0	11.31
IV	3.6	45.24
V	2.5	45.24
VI	0.8	51.87
VII	1.5	43.81

classification of individual cases. In Table 3, therefore, my data have been reduced to a similar form, and the marked contrast between normal increase in weight and that which is found in diabetic individuals is apparent.

This same startling contrast is exhibited in Chart 4, in which Dr. Brathwaite's data on the weight of normal individuals in the third to the seventh decades are represented by the clear columns and the data on my

diabetic patients by the black columns. The height of each column represents the actual average increase in weight in pounds by decades. This is so striking that further comment would be superfluous.

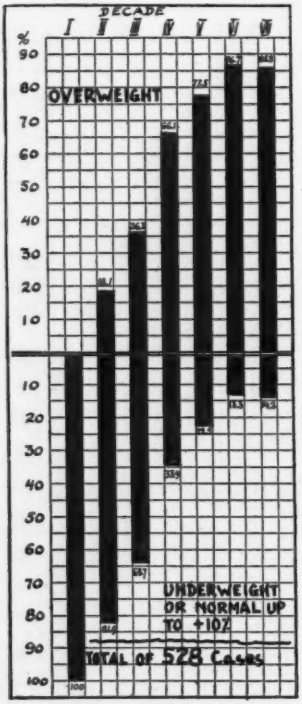


Chart 3.

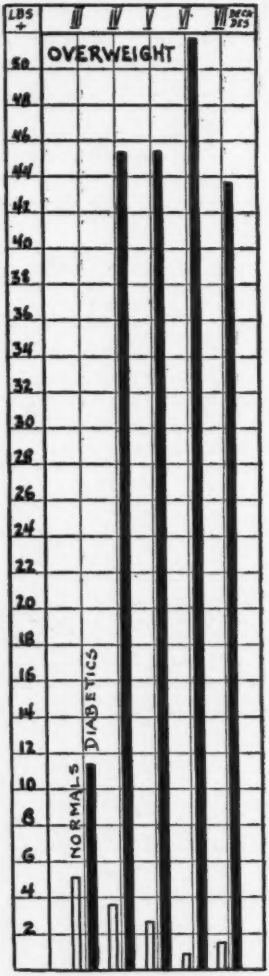


Chart 4.

CONCLUSION

Data are presented which show that diabetic patients personally studied are or have been much overweight. This is strikingly illustrated by comparison with records of a large series of non-diabetics from the files of the Equitable Life Assurance Society. The inference seems justifiable that obesity plays a rather important part in the etiology of diabetes.

The danger of obesity, therefore, should be emphasized to all patients, not only those afflicted with diabetes, for it is a factor which must be reckoned with also in myocarditis, nephritis, arteriosclerosis, apoplexy, and so forth. The public should be warned against the perils of overweight; and the place to begin is not in the office with the middle-aged patient, but in the school, where care of the health rightfully should be taught if the ideal of preventive medicine ever is to be attained.

Book Reviews

AN OUTLINE OF ENDOCRINOLOGY. W. M. Crofton. 1929. William Wood & Company, New York. Pp. 163. 2nd Edition.

Reviewed in Arch. Int. Med. **45**: 823. 1930.

THE INTERNAL SECRETIONS OF THE OVARY. A. S. Parkes, 1929. Longmans, Green and Co., Ltd., London.

Reviewed in Physiological Reviews, **14**: 682. 1930.

Abstract Department

The influence of suprarenin on the galactose assimilation of the liver (Über den Einfluss von Adrenalin auf die Galaktoseassimilation der Leber). Blöch, J., Klin. Wchnschr. **8**: 1707. 1929.

The author describes a test for the estimation of the integrity of the liver parenchyma by the influence of adrenalin on the galactose assimilation. Forty grams of galactose was administered daily for five consecutive days, on the third of which one mgm. of suprarenin was injected subcutaneously at the same time. The galactose elimination in the urine was notably increased on this day in all or a group of ten cases exhibiting catarrhal or neosalvarsan icterus or syphilis with liver involvement. Glucose was not present. Blood sugar curves showed a marked increase in the hyperglycaemia on the suprarenin days. The possible underlying mechanism is discussed.—A. W. R.

Preliminary note on an attempt to concentrate the active principle of the adrenal cortex. Cameron, A. T. and F. D. White, Tr. Roy. Soc. Canada (Sect. V. Biol. Sc.), **22**: 145. 1928.

From several series of experiments the following provisional conclusions are drawn. An active principle of the adrenal cortex, capable of accelerating growth when fed to young white rats, passes into solution during hydrolysis with N/10 hydrochloric acid. The action of this compound is antagonized by adrenine. Such antagonism is overcome by simple oxidation. Methyl alcohol extraction permits concentration. Adrenine, fed continuously to the young rat for a period of 18 days or longer, produces definite toxic effects, including marked inhibition of growth.—A. T. C.

The influence of suprarenal cortex and medulla on the growth and maturity of young (white leghorn) chicks. Eaton, A. G., W. M. Insko, G. P. Thompson and F. E. Chidester, Am. J. Physiol. **88**: 187. 1929.

Chicks fed desiccated suprarenal medulla grew almost the same as the controls for the first few weeks, but after that time their growth was less rapid than the controls. Chicks fed desiccated suprarenal cortex grew much more slowly than the controls at first, but by the end of the first eight weeks they began to grow more rapidly and toward the end of the experiment almost equalled the controls in weight. If the weight of the testes is an indication of maturity, males receiving desiccated suprarenal cortex were more mature than either the controls or those obtaining medulla; those receiving medulla were less mature than those of the other lots.—M. B. G.

Clinical studies in suprarenal therapy. Koehler, A. E. and F. C. McLean, Tr. A. Am. Physicians, **44**: 300. 1929.

This is a brief discussion of a preparation derived from suprarenal glands. It is a highly concentrated preparation advocated in conditions commonly attributed to suprarenal underfunction. A case of myasthenia gravis was also definitely improved by this preparation. One case of Addison's disease treated with this substance resulted in the return of the patient to his occupation for the past 18 months with complete disappearance of symptoms although stopping treatment at various times, was followed by a return of symptomatology within a week. The preliminary observations by these authors lead them to believe that this suprarenal substance has definite therapeutic value in certain cases in which suprarenal substance appears indicated.—I. B.

A case of thymus hyperplasia (Ein Fall von Thymushyperplasie). Laband, A., Monatschr. f. Kinderh. **45**: 225. 1929.

The clinical course in this infant of 2½ months was characterized by cyanosis, stridor, dyspnea and few rales throughout the chest. A diagnosis of pneumonia had been previously made but this was not substantiated by

either x-ray examination or post mortem findings. Death came suddenly. Post mortem examination revealed a thymus which was about one and a half times the size of the heart. The author feels that death was due to mechanical pressure on the large vessels and heart. Small hemorrhages were found in the thymus, heart and lungs.—M. B. G.

Case of hypernephroma with virilismus in a girl of 3½ years. Lundh, G., Acta Paediat. **9**: 118. 1929.

This patient, who first showed symptoms at the age of three years, had over-developed external genitalia, a large clitoris with a hypospadiac formation and marked hypertrichosis. The uterus, vagina, urethra and hymen were normal. Post mortem examination revealed a tumor taking up the place of the left suprarenal gland. Metastases were found in both lungs. Microscopical study showed a tumor built up for the most part of large, richly protoplasmic polyhedral cells with large nuclei, often in the form of giant cells. —M. B. G.

Pathologic histology of adrenalectomized cats. MacMahon, H. E. and R. L. Zwemer, Am. J. Path. **5**: 491. 1929.

The gross and microscopic lesions following experimental adrenal insufficiency in cats (average survival ten days) are described. Briefly, they consist in fatty degeneration of the tubules of the kidney, lymphoid hyperplasia, moderate colloid distention of the thyroid, and hyperplasia of the interstitial cells of the testis. The significance of these, and other observations on experimental adrenal insufficiency, is discussed in relation to "lipoid nephrosis," lymphoid hyperplasia and additional clinical syndromes.—Author's Summary.

The disease picture of interrenalism (Das Krankheitsbild des Interrenalismus). Mathias, E., Med. Klin. **25**: 1879. 1929.

Mathias says that the loss of adrenalin does not explain the disease picture of Addison's Disease. Unfortunately, the suprarenal cortex has long been neglected. Precocious sexuality is frequent in the female with hypernephroma, less frequent in the male. One of the first symptoms noticed in hypernephroma is hairiness and a tendency to acne. Striae are also noticed. In a certain group of cases, polycythemia, hypertonicity, obesity and symptoms of Basedow's disease are present. The presence of striae in interrenalism is of significance in that the striae of pregnancy may be explained on the basis of suprarenal cortex hypertrophy present at this time. Likewise the pigmentation of pregnancy finds an analogy in interrenalism. Signs of interrenalism are also found in acromegaly. The climacterium with the tendency to beard formation, deepening of the voice, tends to show the presence of interrenalism at this time. The author pleads for further research in order to isolate the substance "interrenalin" from the cortex.—R. C. Moehlig.

A case of paroxysmal hypertension associated with suprarenal tumor. Pincoffs, M. C., Tr. A. Am. Physicians, **44**: 295. 1929.

The patient was a married woman of 25, complaining of increasing palpitation for a period of years. The attacks were abrupt in onset, from one to three hours' duration and associated with considerable apprehension, tremulousness and nausea. Between attacks the physical examination was negative but with the onset of the symptoms the systolic blood pressure rose to 260 within a few minutes, while the diastolic pressure did not rise proportionately. The pulse during attacks rose to 110. The urine showed a constant trace of albumin. There was an intermittent glycosuria but the fasting blood sugar was normal excepting during one attack when it rose to 116 mgm. Electrocardiographic studies during the attack showed very high T waves similar to those in acute hyperthyroidism. The diagnosis of medullary tumor of the adrenal was made. Operation revealed an oval tumor of the right suprarenal gland which proved to contain adrenalin in considerable amounts. The pathological diagnosis was pheochromocytoma. Since the day of the operation the patient has never had another attack of paroxysmal hypertension; the systolic blood pressure has varied between 110 and 125 and the patient is apparently in normal health.—I. B.

The hormone of the adrenal cortex (Uber das Inkret der Nebennierenrinde). Schmitz, E. and W. Milbradt, Ztschr. f. d. ges. exper. Med. **68**: 393. 1929.

In previous papers the effect of extracts of the adrenal cortex were examined on pigeons with experimental beri-beri. This substance was called "cortisupren." The effect of this substance is compared with that of interrenin, the hormone isolated by Goldzieher. As first test, the authors examined the effect of both substances upon the blood fats of rabbits. They confirmed Goldzieher's observations that interrenin decreased the concentration of cholesterol and phosphorus containing lipoids, as well as that of fatty acids. The effect of cortisupren was identical, so far as cholesterol and fatty acids are concerned, but it increased the phosphatids in contradistinction to interrenin. In pigeons fed on rice the development of beri-beri is accompanied by a tremendous rise of the blood fats. If interrenin is given, the rise of cholesterol and fatty acids can be checked and that of phosphatids completely prevented. The effects of cortisupren are less distinct and negligible in relation to the phosphatids. The authors claim that cortisupren contains apparently another substance besides interrenin, which affects the phosphatids of the blood in a different way. The absence of adrenalin or choline in both preparations used could be demonstrated.—M. B. G.

The functional diagnosis of adrenal disease (Zur Frage der funktionellen Diagnostik der Nebennieren). Tschebokssarow, M. N. and S. J. Malkin, Endokrinologie, **5**: 331. 1929.

The authors describe a diagnostic procedure for the definition of adrenal disease on the basis of the selective differential inhibition of "serum" and "adrenal" lipase by quinin, chloral hydrate and atoxyl. A few laboratory protocols are tabulated and two illustrative cases briefly described, in the second of which a diagnosis of hyperadrenalism is based upon the patient's response to an adrenalin test and the condition successfully treated with insulin.—A. W. R.

The hypoglycaemia of Addison's disease (Über Hypoglykämie bei Morbus Addisonii). Wadi, W., Klin. Wchnschr. **7**: 2107. 1928.

The author discusses the conventional allocation of low blood pressure and blood sugar, asthenia and pigmentation to medullary insufficiency and the gastro-intestinal disturbances, delirium, convulsions, collapse, and coma to the failure of cortical function. Most of the latter are associated with the terminal phase of Addison's disease but the author contends that they arise from the hypoglycaemia and draws a parallel with the symptoms of insulin poisoning. He gives the protocol of a careful investigation on a single case. Suprarenin injection produced a notable fall in blood sugar associated with the features of a terminal condition which were relieved by glucose administration. Recurrence of the symptoms, recorded on several subsequent occasions, was always associated with low blood sugar, and except in the last and fatal attack, relieved by glucose. He concludes that the so-called "cortex symptoms," exclusive of the gastro-intestinal disturbances, are referable to the hypoglycaemia.—A. W. R.

Pneumin. A respiratory autacoid from the adrenal cortex discharged into the circulation via the lymphatics. Vincent, S. and J. H. Thompson, J. Physiol. **67**: 3. 1929.

In decerebrate cats complete adrenalectomy performed after elimination of all anaesthetic was found to result in death from respiratory failure. Similar effects were observed when damage was done to the posterior region of the glands, and more careful investigations revealed a lymphatic plexus in this area, ligature of which caused respiratory failure. Ligature of the adrenal veins was without effect. Removal of the lymph glands into which the plexus drains, or ligature of the lymphatic trunks in the neck, brought about all the typical signs of cortical insufficiency in the decerebrate cat. Numerous and varied control experiments were made. The conclusion was reached that some autacoid, which the authors propose to call pneumin, is discharged from the adrenal body by way of the lymphatics and is essential to normal respiration in decerebrate cats. Extracts of the cortex completely restored respiration after cessation due to adrenalectomy. Experimental evidence is given to prove that the medulla is not concerned.—J. H. Thompson.

The endocrine mechanism of fever and heat regulation (Der Endokrine Mechanismus des Fiebers und der Warmeregulation). Cramer, W., Endokrinologie, **4**: 25. 1929.

An abstract of a book by the same author. Using histological evidence as a basis, the author reaches conclusions similar to those reached by physiological methods, e. g., cold stimulates excretion of adrenalin and thyroxin into the blood stream, thus maintaining body temperature. If the cold stimulus persists too long, the gland is emptied, the body temperature falls and the animal dies. The conditions of the glands are quite evident in histological sections. Gland action may be stimulated also by certain chemical substances. When such stimulation occurs in a normal animal the increased output produces fever. Fever of this type might be aseptic. Temperature regulation on the internal part of the body is thus correlated to temperature changes external to the body through the medium of the adrenal and thyroid glands. The sympathetic system is involved, of course, due to its action on sweat glands and pilomotor muscles.—B. C.

Keratoconea of endocrine origin (Un cas de keratocone d'origine endocrinienne corrige par l'opotherapie pluriglandulaire). Meerhoff, W., A. Meerhoff and J. M. Pareja, Rev. franç. d'endocrinol. **7**: 399. 1929.

This is the case of a child who had an adiposo-genital syndrome of the Babinski-Froehlich type aggravated at the same time by a bilateral keratoconea. The evolution of the glandular dystrophy and its yielding to well conducted pluriglandular opotherapy alone, without treatment of any other kind, resulted in improvement of ocular, somatic, functional, mental and cardio-vascular conditions.—J. Gagnon.

Endocrine and fatigue headaches. Stevens, N. C., New England J. M. **201**: 801. 1929.

This paper is largely devoted to a discussion of migraine which is regarded as being of endocrine origin. It is frequently associated with a low metabolic rate and in such cases responds to thyroid by mouth. The menstrual type is sometimes ameliorated by ovarian extract over a prolonged period.—J. C. D.

Endocrine tumours. Weber, F. P., Brit. M. J. **1**: 105. 1929.

In general, endocrine tumours may be divided into 2 groups, (1) a pathological but compensatory reaction to supply a specific hormone deficiency, and (2) true neoplasms which occur independent of any need or stimulation. Tumours of the pineal and of the interstitial cells of the testis may give rise to macrogenitosomia, while growths of the adrenal cortex, anterior pituitary, pineal or interstitial cells of the testis or ovary may produce precocious growth or precocious sexual development. Associated with nodules in the malpighian bodies of the spleen there may be anaemia, thrombocytopenia, and a tendency to haemorrhage. A number of cases are discussed.—Wm. Susman.

The regulation of metabolism. XII. The special position of carbohydrate constituents in rapidly growing cells [Embryonic and tumor cells] (Stoffwechselregulationen. XII. Die Sonderstellung der Kohlehydratbestände in Zellen mit Starker Wachstumsfähigkeit [Embryonal- und Geschwulstzellen]). Wertheimer, E., Arch. f. d. ges. Physiol. **223**: 619. 1929. Abst., Physiol. Absts. **15**: 109.

When pregnant rats or guinea-pigs are rendered glycogen-free by means of cold or adrenalin, the glycogen content of the embryos and of the maternal uterus is unchanged or very little decreased. On injecting adrenalin into new-born animals (2 to 15 days old), marked stability of the glycogen stores is observed. Although the doses used were several times greater than those necessary to bring about a maximal glycogen loss in adult animals, the glycogen loss in the new-born animals was either nil or relatively small; it rose with increase in the age of the animals. Mouse carcinoma cells of Ehrlich contain only traces of glycogen or free sugar. The greater part of the total carbohydrate content (0.19 to 0.25%) is only set free after acid hydrolysis.

When the host organism is deprived of glycogen by means of cold, oxygen lack, or strychnine poisoning, or by the action of adrenaline, insulin or thyroxine, the carbohydrate content of the carcinoma cells remains unchanged. The overfeeding of these animals with carbohydrates brings about an increase in the carbohydrate content of the tissues, but not of the carcinoma cells. Similar results were obtained with rat sarcomata of Jensen. It is concluded that the carbohydrate stores of cells, which tend to multiply rapidly, are not under the control of the whole organism, and can only be metabolised by the growing cells themselves, independently of the organism.

The nature of a substance occurring in the serum of animals rendered anemic which influences corpuscular count (Uber die Natur der Blutkorperchenzahl beeinflussenden Substanz in Serum anamisierter Tierre). Zih, A., Endokrinologie, **3**: 81. 1929.

A substance was secured from the serum of animals which were made anemic by methods previously described and from which the spleen had also been removed, which had a marked effect on the corpuscular count. It either increased or decreased the red cell count, depending chiefly on the dosage. —B. C.

Influence of age of graft and receptor on oestrous cycle (Influencia de la edad del animal receptor y del ovario injertado sobre el ciclo oestrual de la rata blanca). del Castillo, E. B., Rev. Soc. argent. de biol. **5**: 271. 1929. Abst., Physiol. Absts. **15**: 119.

The grafting of an ovary from an adult rat to an adult castrate produces prolonged oestrus, interrupted by short dioestrus, then gradually dioestrus becomes longer and less regular than in normal animals. Ripe follicles and corpora lutea are found as much as 18 months after grafting. Ovaries from immature rats grafted into adult castrates produce a small number of cycles with gradually increasing dioestrus; soon dioestrus becomes permanent. Post-mortem examinations show that the graft has been completely reabsorbed. Adult ovaries grafted into immature castrates are reabsorbed; the vagina opens at the normal time, but no oestrus occurs. The most important factor is the age of the receptor organism; the age of the graft has a certain influence. Optimum conditions obtain when the graft coming from an adult is put into an adult.

Culture of mammalian testicular tissue and the nature of the interstitial tissue and interstitial cells (Über Kulturen des Hodengewebes der Säugetiere und über die Natur des interstitiellen Hodengewebes und der Zwischenzellen). Esaki, S., Ztschr. mikr. anat. Forsch. **15**: 368. 1928.

From the behavior of tissue cultures of the testes of young normal and experimental cryptorchid guinea pig to vital dyes it is concluded that interstitial cells are quite distinct from resting wandering cells or histiocytes. At the periphery of the culture, the interstitial cells may change into spindle-shaped cells indistinguishable from ordinary fibroblasts. The flattened cells of the walls of the tubules are mesenchymal elements which can change into either interstitial cells or into histiocytes. Interstitial cells under favorable conditions may change into mature fibroblasts. Sertoli cells also grow out from opened tubules as spindle-shaped cells indistinguishable from fibroblasts. Some Sertoli cells change into round or polygonal phagocytic elements.—A. T. R.

Lipoid-soluble and lipoid-insoluble forms of the ovarian hormone (Über lipoidlösliche und lipoidunlösliche Formen des Ovarialhormons). Glimm, E. and F. Wadehn, Biochem. Ztschr. **207**: 361. 1929.

Hormone was extracted from urine of pregnancy with ether. Repeated extraction removed only about three-fourths of the active material. Remainder seemed ether-insoluble. Heating the urine with alkali increased the proportion of ether-insoluble hormone, with considerable loss of total activity. Heating with acid reversed this reaction to some extent, causing the ether-insoluble active material to become ether-soluble. Similar results obtained with purified preparations of ovarian hormone.—B. S. Walker.

Isolation of female sex hormone (Über einige Versuche zur Isolierung des weiblichen Sexualhormons und über dessen Fällbarkeit mit Antimonpentachlorid). Goldhammer, H., Biochem. Ztschr. **215**: 1. 1929. Abst., Physiol. Absts. **15**: 118.

Placental extract in chloroform solution gives a blue color with antimony trichloride, which is characteristic for the mixture, but not for the hormone itself; antimony pentachloride precipitates the hormone itself. By treatment of this precipitate with sodium hydroxide the hormone may be isolated in an odorless and very active form from the unsaponifiable chloroform extract of the urine of pregnancy as well as from the placenta. Under certain circumstances the hormone becomes water-soluble.

Effect of ovarian hormone on sex of offspring (Demerkungen zur experimentellen Hyperfeminierung). Gostimirovíc, D. Klin. Wchnschr. **8**: 2091. 1929. Abst., Physiol. Absts. **14**: 663.

The results are tabulated of 55 litters from 50 mice that received "folliculin-menformon" in doses of 0.5 mouse units per day for 6 to 7 days before mating. The ratio of male and females in the litters of the controls was 1.08:1, and in the experimental animals 1.32:1.

Aschheim-Zondek's pregnancy reaction: Its significance in differential diagnosis of amenorrhea and menopausal disturbances (Die Aschheim-Zondeksche Reaktion und ihre differentialdiagnostiche Bedeutung für Amenorrhea und Klimakterium). Solms, E. and E. Klopstock, Deutsche med. Wchnschr. **55**: 1919. 1929. Abst., J. A. M. A. **94**: 300.

Aschheim-Zondek's pregnancy test was employed in 349 cases. The results were correct in more than 99 per cent. Further experimentation with the method convinced the authors that it is of diagnostic and therapeutic value in cases of amenorrhea and in menopausal disturbances. It has been proved that these conditions are caused either by hyperfunctioning or by hypofunctioning of the endocrine sex glands. The changes in the test animals reveal which of the two conditions is the etiological factor in each instance. In cases of hypofunctioning the therapy then supplies the missing hormones, whereas in cases of hyperfunctioning preparations that have an antagonistic effect on the hormonal secretions are administered. The authors describe four cases that show the value of this method.

Concerning the mammary gland secretion in the male. A contribution to the problem of intersexuality (Über Brustdrüsensekretion beim Manne. Ein Beitrag zum Problem der Intersexualität). Levinger, E., Ztschr. f. d. ges. Neurol. u. Psychiat. **116**: 559. 1928.

Levinger reports a case of a young man, nineteen years of age, suffering with bilateral tuberculosis of the productive type. The family history revealed that the father was an alcoholic and two sisters had died of tuberculosis. The patient had suffered from the disease for six years and had suffered from bedwetting until the age of nine years. As a child he sucked his fingers, played with dolls and loved to cook. Puberty developed normally. He had no homosexual tendencies. The physical examination revealed a very pale young man. The secondary sex characteristics were normal. The right nipple was less developed than the left and erectile contraction of the nipples was produced by mechanical irritation. The testes were normally developed, the thyroid was normal and there was marked dermographism. X-ray examination of the sella turcica revealed that it was somewhat smaller and deeper than usual. The patient's general configuration gave one the impression of feminine characteristics. The patient had noticed that the breasts felt full and on examination pressure brought forth white fluid which showed, microscopically, colostrum. It was also noticed that there was an accessory nipple above the right nipple. Levinger then takes up in detail some of the conditions which may produce milk secretion in the male breasts. He also discusses the relationship of the different endocrine glands to development of the breasts and their function. Examining forty male individuals suffering with tuberculosis, ranging in age from eighteen to forty-five years, he found three cases of milk secretion in the male breasts. All three had true colostrum as verified by microscopic examination.—R. C. Moehlig.

The chemistry of oestrin. I. Preparation from urine and separation from an unidentified solid alcohol. Marrian, G. F., Biochem. J. **23**: 1090. 1929. Abst., Physiol. Absts. **15**: 117.

Urine collected 1 to 2 weeks before parturition was extracted with ether, the extract washed, and the ether evaporated. The residue was saponified with KOH and the unsaponifiable matter extracted with ether. After evaporation of the ether, the residue may be treated with a little ether or acetone, which removes the oestrin, and the saponification of this extract repeated. For large quantities of urine it was convenient to use toluene as a preservative and also to break the emulsion formed when extracting the saponified material. The solid alcohol, being only slightly soluble in ether or acetone, was left behind, and the oestrin was extracted from the final residue. When chloroform was used instead of ether, the alcohol was not obtained, but caffeine appeared in the final residue. The alcohol crystallizes in white plates, has m.p. 233° to 235°, is only slightly soluble in organic solvents and insoluble in water, is not precipitated by digitonin, does not give sterol color tests, but shows a deep brown color with acetic anhydride and H_2SO_4. It has not oestrin activity. From analysis and molecular weight determinations its formula appears to be either $C_{19}H_{32}O_2$ or $C_{20}H_{34}O_2$; it forms a diacetate, and is therefore a dihydroxy alcohol; it is saturated compound. It was not found in healthy male and non-pregnant female urine. The yield of oestrin from urine was up to 1,800 mouse units per liter of activity 0.0183 to 0.0016 mgm. per unit; the yield of the alcohol was from 0.02 to 0.2 g. per 100 liters.

The chemistry of oestrin. II. Methods of purification. Marrian, G. F., Biochem. J. **23**: 1233. 1929. Abst., Physiol. Absts. **15**: 117.

The unsaponifiable ether-soluble fraction obtained from urine (0.00357 mgm. M. U.) was fractionated with 70 p.c. and then 50 p.c. alcohol, without loss of activity and with definite purification; after the first treatment the unitage was 0.00167 mgm., and after the second 0.00106 mgm., the activity being in the soluble fraction. From an ethereal solution of the latter, about ⅔ of the activity was extracted by 4.8 p.c. KOH, the resulting unitage being 0.000135 mgm.; part of the activity remained in the fractionation. Oestrin is stable to boiling aqueous alkali and sodium chloride, but is destroyed by ether peroxides. It can be extracted by ether from neutral or acid aqueous solution completely, from alkaline solution only incompletely. If an alkaline solution has CO_2 bubbled through it, ethereal extraction becomes complete. The purest fraction was soluble in lower alcohols, acetone, ethyl acetate, and chloroform; slightly soluble in ether, benzene, hexone, 30 p.c. alcohol, and water. On diluting an alcoholic solution with water and evaporating off the alcohol, two-thirds of the activity was precipitated.

Temporary sterility of the wife following the hypodermic injection of sperm from the husband (Sur la question de la sterilite temporaire de la femme a la suite de l'injection hypodermique de sperme du mari). Naiditch, M. S. and Mme. N. A. Zaitseva-Kalinovskaya, Russian J. Endokrinol. **3**: 140. 1929.

The authors have not been able to cause temporary sterility in the wife by subcutaneous injection of sperm of the husband, and do not recommend the method because of the difficulty of obtaining living spermatozoa in a sterile state. For the production of spermotoxins, the use of human spermatozoa presents no advantages over the use of animal spermatozoa.—M. O. L.

Anterior pituitary-implantation in Rhesus (Hypophysen-orderlappen-implantation in Rhesusaffen). Ehrhardt, K., H. Weisbader and L. Foesaneanu, Endokrinologie, **3**: 401. 1929.

Two Rhesus monkeys, observed for 6 months, showed regular menstrual periods. One ovary was removed from each and examined macro- and microscopically. No sign of corpus luteum was found. Pituitary implants were then made. This was followed by an enlargement of the uterus and the usual livid coloring. The second ovary was removed and examined, but corpus luteum was not found. These authors suggest the use of these animals in studying the effect of the pituitary hormone upon the follicular part of the ovary.—B. C.

The effect of daily transplants of the anterior lobe from gonadectomized rats on immature test animals. Engle, E. T., Am. J. Physiol. **88**: 101. 1929.

Experiments were conducted on 62 rats of both sexes, one group being gonadectomized at the age of 20-30 days and the second at one year of age. The animals were sacrificed eight months after the operation and their pituitaries transplanted on successive days into immature mice and rats. A control group received the glands from normal non-gonadectomized rats. Results indicate that the anterior lobe of rats which have been gonadectomized for eight months contain a greater supply of gonadal stimulating hormone than occurs in the normal animal. This is shown by the earlier sex maturation and increased size of the ovaries of the test animals receiving transplants from the castrated animals. This would seem to indicate that the anterior lobe continues to elaborate gonad stimulating hormone even after castration. There is no sex difference in the biological potency of the gland of gonadectomized donors and no significant difference as regards the age of the donor at the time of gonadectomy.—M. B. G.

Does cerebro-spinal fluid contain anterior lobe pituitary hormone (Liquor und Hypophysen-vorderlappenreaktion)? Erhardt, K., Klin. Wchnschr. **8**: 2330. 1929. Abst., Physiol. Absts. **15**: 48.

Using the Zondek-Aschheim reaction, the cerebro-spinal fluid obtained by lumbar or suboccipital puncture was tested for the presence of the active principle of the anterior lobe of the pituitary. Neither from normal children, adults nor from cases of disease of the gland was a positive reaction obtained. In pregnancy the reaction was also negative.

Pituitary implantation and sexual stimulation in toads (Implantación de la hipófisis y estimalación sexual en el sapo). Houssay, B. A. and J. M. Lascano-Gonzalez, Rev. Soc. argent. biol. **5**: 397. 1929. Abst., Physiol. Absts. **15**: 116.

Subcutaneous implantation of the glandular lobe of the pituitary produces (a) in males stimulation of the testicles, as seen by increase in weight and spermatogenesis, and of the central nervous system, as seen by copulatory embracing out of season; (b) in females, ovulation with expulsion of eggs. This effect is only obtained with toad pituitary; it is not obtained with the pituitary of mammals, birds, snakes, and frogs, nor with pregnant women's urine. The active principle is destroyed by heating, and is insoluble in alcohol and acetone. The anterior pituitary conditions the growth and maintenance of the gonads, and therefore the secondary sexual characters.

Pituitary tumor with goiter and acromegaly. Ironside, R., Proc. Roy. Soc. Med. **23**; 6. 1929. (Sect. Neur.)

The patient was a woman of 60 who, 25 years before, began to take larger shoes and gloves and to notice a swelling of the neck. An operation had been performed 15 years before for substernal goiter on account of dyspnea. This had resulted in residual paralysis of the left recurrent laryngeal nerve. The patient now presented distinct evidences of acromegaly with headache, hypertrophic changes in the joints of the limbs, enlargement of the sella turcica, and enlargement of the supraclavicular lymphatics and of the submaxillary glands. There were characteristic alterations in the fields of vision, hemorrhages in both fundi, and arterial hypertension.—I. B.

Acromegalic diabetes (Le diabète acromégalique). Martin, E., Rev. méd. de la Suisse Romande, **49**: 693. 1929.

Pituitary patients often have difficulties in sugar metabolism. Acromegalic diabetes is not completely explained either by the hyperglycemic action of the pituitary hormone or by a tumoral compression of the infundibular nerve centres, but is more probably explained by the neurocrinic effect of a hypophysis in hyperfunction associated with changes of the endocrine pancreas. The "neurocrine" seems to be a type of secretion of great interest since it explains the histo-physiological correlations of an endocrine gland and the sympathetic system. In certain cases of diabetes if the pancreas is the principal cause of

the illness the changes in the other endocrine glands cause us to speak of pluriglandular diabetes. These cases help us in understanding acromegalic diabetes and the role and interdependence of the endocrin-sympathetic system in the equilibrium of the sugars.—J. Gagnon.

The possibility of estimating the size of the sella turcica (Über die Moglichkeit einer objektiven Grossenbestimmung der Sella Turcica). Sartorius, W. Monatschr. f. Kinderh. **45**: 259. 1929.

The author studied the size of the sella turcica in 100 normal children between the ages of 1 and 10 years and presents a curve which demonstrates an increase in the size of the sella turcica in direct proportion with the age. No reference is made to previous American work on this subject.

—M. B. G.

Investigations of the functions of the anterior lobe of the hypophysis: the influence of extracts of the anterior lobe upon the genital apparatus and flow of milk in the rabbit (Recherches expérimentales sur les fonctions du lobe antérieur de l'hypophyse: influence des extraits du lobe antérieur sur l'appareil génital de la lapine et sur la montée laiteuse). Stricker, P. and F. Grueter, Presse méd. **37**: 1268. 1929.

Aqueous extracts were prepared from anterior pituitaries and injected into female rabbits, (1) immature, (2) virgin adults, (3) spayed adults, (4) pregnant, (5) pseudo-pregnant. Immature rabbits were given injections of aqueous extract equivalent to 0.5 gm. of anterior pituitary. Second injections were given 24 or 48 hours later. On the fourth or fifth day the ovaries were greatly enlarged and congested. There was enlargement of follicles with hemorrhage in some and even formation of corpora lutea in some. If a series of 6 to 12 injections was given the reaction was intense and the ovaries resembled a bunch of grapes. There were then found ripe follicles, atretic follicles, hemorrhagic follicles and corpora lutea in various stages of development. The uterine horns were enlarged and congested and sections showed the lutein phase in which the mucosa is prepared for the nidation of the ova. In normal adult females after 4 to 8 injections of extract, equivalent to 1 gm. or 1.5 gm. of anterior lobe in each dose, the ovaries were found to contain as many as 30 corpora lutea and 15 to 20 hemorrhagic follicles. The uterine horns were greatly thickened. Rupture of follicles in rabbits in heat was brought about by one injection of anterior pituitary extract in the absence of coitus. Ovariectomized adults reacted differently than normal females to injections of anterior pituitary extract. The uterine horns were congested but the mucosa did not show the changes essential for nidation of the ova. The mammary glands, however, were influenced by the injections. Normal adult females in heat were mated with males which had been rendered improcreant by vasoligation. On the 10th day after the infertile coitus the development of the uterus, corpora lutea and mammary glands had reached the maximum. Extract of anterior pituitary was then injected 4 or 5 times. On the 18th or 20th day the animal was killed and the ovaries were found to be extremely congested and filled with atretic follicles, hemorrhagic follicles and corpora lutea, 25 to 45 per ovary. The uterine mucosa had not been allowed to return to the resting stage but had remained in the stage of proliferation ready for nidation of ova. There was also an abundant secretion of milk from the mammary glands although the animals were not pregnant. Immature rabbits (6-8 weeks old, weighing 900-1200 gm.) were given 4 to 6 injections of an aqueous extract of anterior pituitary. Each dose corresponded to 1 gm. to 1.5 gm. of fresh gland. The ovaries were found to contain mature follicles, hemorrhagic follicles and corpora lutea but the mammary glands did not show any appreciable change. It seems possible then that the mammary gland can react to anterior pituitary hormone only when it has been influenced by some specific substance which is found only in an adult animal. This specific substance may be the hormone of the corpus luteum. Rabbits in heat were submitted to infertile coitus and 8 to 10 days later were given 2 or 3 injections of anterior pituitary extract. In 2 to 4 days after the first injection a flow of milk began. When the injections were continued for 7 to 8 days the mammary glands became engorged with milk. It is possible that the mammary gland secretion was conditioned by the intense activity of the ovaries. In order to rule out this factor another experiment was performed in which rabbits were ovariectomized on the 10th day after infertile

coitus. Injections of anterior pituitary were started on the day of operation or the following day. The flow of milk occurred 2 or 3 days after the first injection and became very abundant by the 6th to 10th day if the injections were continued. There was no effect on the genital tract and the uterine horns showed castration atrophy. In one rabbit, ovariectomized after infertile coitus, the mammary glands were allowed to atrophy for 3 months. Upon injecting anterior pituitary extract the mammary glands became active again and secreted milk. No success was had in provoking the flow of milk in ovariectomized rabbits unless there had been either fertile or infertile coitus previous to the injections of extracts of anterior pituitary. Injections of folliculin in addition did not alter this finding. In pregnant animals injections of anterior pituitary extracts caused a flow of milk but also caused abortion. In only one experiment secretion of milk took place without the death of the fetus. In a normal female which had nursed her young and weaned them and had been without milk for two weeks, the flow of milk was started up again by a single injection of anterior pituitary extract. A dog under quite similar conditions was able to nurse two adopted puppies for several days.—E. P. Bugbee.

Effects of feeding silkworms on extracts of the anterior lobe of the pituitary gland. Thompson, J. H., Arch. f. Entwcklngsmechn. d. Organ. **114**: 578. 1928-29.

Feeding silkworms on fresh lettuce leaves soaked in an extract of the anterior lobe of the pituitary (Parke, Davis & Co.) caused marked retardation in growth, delayed metamorphosis and increased the mortality at the various stages of metamorphosis. Not a single experimental animal reached the complete chrysalis stage. The circulation was slowed. The author believes that these effects are due to a failure of metabolism, especially of carbohydrates.
—A. T. R.

Carbohydrate metabolism in acromegaly. Wishnofsky, M. and C. S. Byron, J. Lab. & Clin. Med. **15**: 216. 1929.

The disturbance in carbohydrate metabolism in acromegaly may be incidental to or concomitant with diabetes mellitus. Of cardinal importance is the fact that although pituitrin neutralizes the effect of insulin on blood sugar concentration, it does not affect the action of insulin on the oxidation mechanism of glucose. This fact may be utilized in determining the nature of the carbohydrate disturbance. If after the administration of a large quantity of glucose the respiratory quotient fails to approach 1, diabetes mellitus is present; if the respiratory quotient does approach unity, the glycosuria is symptomatic regardless of its degree.—I. B.

Further investigations upon the preparation, biological actions and clinical uses of Prolan, the hormone of the anterior lobe of the hypophysis (Weitere Untersuchungen zur Darstellung, Biologie und Klinik des Hypophysenvorderlappenhormons [Prolan]). Zondek, B., Klin. Wchnschr. **8**: 157. 1929.

Zondek details further investigations made by himself and Aschheim on the effect of the hormone of the anterior lobe of the pituitary gland ("Prolan") on the genital apparatus. In contrast to the ovarian hormone it is destroyed by heat, strong acids and alkalis, while it is insoluble in most solutions which dissolve lipoids. Previously biological tests have been confined to mice and rats, but the author has now used guinea-pigs. "Prolan," 2 to 4 cc., equivalent to 60 to 120 rat units, was injected for 10 to 14 days and caused considerable changes in the sexual organs. The uteri increased in size from thin tubes to the thickness of a finger, became livid blue in color and gave the appearance of early pregnancy. The ovaries increased in size to that of a cherry stone and showed multiple haemorrhagic areas with corpora lutea. Microscopical examination of the uterine mucosa revealed hypertrophy similar to the changes during pregnancy. The ovaries manifested luteinization with hindrance of ripening of the follicles. Eventually "Prolan" was concentrated so as to contain 30 rat units per cc. and 60 units was considered to be the minimum dose for human beings. The author has found that the injection of 3 cc. is followed by a definite increase in cholesterin in the blood. When it is injected intramuscularly, hyperaemia of the genital tract occurs as in pregnancy. The temperature of the pelvic organs varies from 0.5° to 1° C. higher

than that taken in the axilla. Possibly this effect may prove of value in the treatment of inflammatory conditions of the pelvis. If "Prolan" be injected from the first day of menstruation and continued until the eighth day of the cycle, microscopical examination of the uterine mucosa reveals changes equivalent to those found usually from the fourteenth to sixteenth days. Changes in the ovaries have been observed, but the connection with the injections has not yet been established. While in two instances milk secretion was provoked, this was not found to occur in the majority of cases. Ten patients with amenorrhoea due to glandular deficiency have been treated. In two instances after daily injections for six days and following on an interval of a week, curettage revealed a mucosa with prolific glandular formation and commencing secretion. In five patients menstruation began from seventeen to thirty days after injections and recurred in three to four weeks. Further work remains to be done to determine the dosage and length of administration to insure a permanent rhythm. The author's results with oral administration are not satisfactory and may be due to the smallness of the dose or the destruction of the hormone in the stomach and intestines. While with the rat the oral route is successful, this is not so with mice, even in larger doses.—E. P. Bugbee.

The diagnosis of pregnancy by the demonstration of the hormone of the anterior lobe of the pituitary in the urine (Die Schwangerschaftsdiagnose aus dem Harn durch Nachweis des Hypophysenvorderlappenhormons). Aschheim, S. and B. Zondek, Klin. Wchnschr. **7**: 1404. 1928.

In previous work Aschheim and Zondek pointed out the physiologic action of the anterior lobe hormone of the pituitary upon the development of the ovary of the infantile white mouse. They have observed three reactions: (1) Ripening of follicles, ovulation, and oestrus; (2) "blood spots" (hemorrhagic follicles); (3) luteinization of follicles and formation of corpora lutea atretica. These reactions could be provoked only by the anterior lobe of the hypophysis from either sex and the authors conclude that this hormone is the one specific sex hormone. They found also that this hormone is stored in the decidua, placenta and corpus luteum of pregnancy as these substances when introduced into test mice produced the above-mentioned anterior lobe reactions. Further investigations showed this hormone to be present in the blood serum and urine of pregnant women, the urine containing the larger amount of the active principle. Subcutaneous injections of small doses of urine produced the characteristic changes in the ovaries of the test mice. Since urines of non-pregnant individuals caused no reaction the authors conclude that this forms a reliable means for the diagnosis of pregnancy. For this test the authors use at least 5 infantile female mice 3-4 weeks old and weighing 6-8 grams. The morning urine is most desirable since it contains the hormone in greatest concentration. Six injections are given in the course of three days, the dosage ranging from 0.2-0.4 cc. At the end of 100 hours the mice are autopsied and the reaction of the ovaries observed. In the majority of instances a correct diagnosis could be made macroscopically but whenever the reaction was doubtful a microscopic tissue examination was necessary. A definite positive reaction is easily recognized by the presence of "blood spots" but a negative reaction must always be checked microscopically. Enlargements of the uterine horns and the presence of a positive Allen test (changes in the vaginal mucous membrane indicating oestrus) are due to the presence of ovarian hormone and are not diagnostic of pregnancy. The ovarian hormone results either secondarily to the action of the anterior lobe hormone upon the mouse ovary or has been introduced directly with the urine. Reactions 2 and 3 are essential to the diagnosis of pregnancy, i.e., formation of "blood spots," luteinization of follicle epithelium and the development of corpora lutea atretica. The presence of one hemorrhagic follicle, one luteinized follicle or one corpus luteum atreticum suffices for the positive diagnosis. The anterior lobe hormone was found in greatest amounts during the early months of pregnancy and gradually decreased in amount as pregnancy approached full term and disappeared after the first few days of the puerperium.—H. C. Mack.

The influence of insulin and epinephrin on glycogen formation in the liver. Cori, C. F. and Gerty T. Cori, J. Biol. Chem. **85**: 275. 1929.

Deposition of liver glycogen during a continuous intravenous injection of a large excess of glucose was determined in nephrectomized rats under amytal

anesthesia. For an equal quantity of glucose injected, the insulinized animals showed a blood sugar level and a glycogen content of the liver approximately one-half of that of the control animals. When a similar blood sugar level was maintained in control and insulinized animals by injecting less glucose into the former than into the latter, there was no difference in the amount of glycogen deposited in the liver of the two groups of animals. It was concluded that the blood sugar concentration is a factor determining the rate of glycogen formation in the liver. When epinephrine was injected, less glycogen was formed than in the control animals receiving the same amount of glucose, in spite of the fact that the blood sugar level of the former animals was nearly twice as high as that of the latter. The low glycogen content of the liver was ascribed to a preponderance of mobilization over new formation of live glycogen in anesthetized animals receiving epinephrine injections.—Authors' Abst.

Duration of anticoagulant action of heparin in vivo in relation to dosage. Gross, P., Proc. Soc. Exper. Biol. & Med., **26**: 383. 1929.

The intravenous injection of heparin is followed by an immediate increase in clotting time. The rate of return toward the normal clotting time is very rapid for one-third of the duration of the heparin action, and subsequently, more slowly. In general, there is an approximate relationship, as expressed by a graph, between the dose of heparin per kgm. of body weight and the duration of the heparin effect in rabbits.—M. O. L.

Diabetes with hypertrophy of the cortex of the suprarenals. Chiari, H., Wien. klin. Wchnschr. **42**: 1318. 1929.

A man, 54 years old, with diabetes, died in coma, despite the use of 100 units of insulin with 40 grams of glucose intravenously. Necropsy showed gangrenous pneumonia of the upper lobe of the left lung, certain atrophic changes in the pancreas, and marked hypertrophy of the suprarenal cortex. The suprarenal glands weighed 20 grams each, and the cortex measured four to five millimeters in thickness. The enlargement was not the result of adenomatous growths. Microscopically, there was a marked diminution of fatty substance in the cortical cells. The author discusses various facts and theories concerning the relationship between the changes in the cortex of the adrenals and those in the pancreas and the effect of the former on blood sugar, but was unable to come to a satisfactory conclusion.—H. Ulrich.

Hyperglycemia following the portal injection of insulin. Collens, W. S. and J. R. Murlin, Proc. Soc. Exper. Biol. & Med. **26**: 485. 1929.

There was a transient rise in blood sugar obtained five minutes following the portal injection of insulin. The dose of insulin employed was .05 and 0.1 unit per kilo of body weight. The results seem to indicate that one of the functions of insulin, if given in large enough dosage, is a glycogenolytic one.
—W. S. Collens.

Diabetes in the tuberculous. Crow, S. L., Southern M. J. **22**: 1079. 1929.

Six cases are described. The author concludes: (1) Tuberculosis is probably no more frequent in diabetics than in non-diabetics. (2) When these two diseases co-exist, tuberculosis is usually the complication. (3) Best results are obtained when diabetes is given first importance; therefore maintenance of a normal glycemia is the ideal goal of treatment. (4) As a result of the better management of diabetics, the prognosis of cases complicated with tuberculosis has been greatly improved.—J. C. D.

Diabetic coma—then and now. Fitz, R., New England J. M. **202**: 967. 1929.

This paper gives specific rules for meeting this condition and a study of cases. Coma is preventable in most cases, can be treated with excellent prospects by insulin, and does not represent necessarily a terminal condition.
—J. C. D.

Studies in carbohydrate metabolism. VI. The antagonistic action of pituitrin and adrenaline upon carbohydrate metabolism, with special reference to the gaseous exchange, the inorganic blood phosphate and the blood sugar. Lambie, C. G. and F. A. Redhead, Biochem. J. **23**: 608. 1929. Abst., Physiol. Absts. **14**: 650.

One cc. pituitrin subcutaneously in man postpones the rise in metabolism produced by injecting intravenously 20 g. glucose or dihydroxyacetone; the increase is greater with the latter than with glucose, and occurs earlier; pituitrin delays its maximum without postponing the onset, as in the case of glucose. The rise in metabolism produced by 10 to 15 units of insulin is usually abolished by 1 cc. pituitrin, which alone usually decreases the metabolism, although raising the respiratory quotient. Pituitrin raises the blood sugar and counteracts the fall due to insulin, but usually causes a fall in blood inorganic P. The effects of adrenalin are in certain respects similar to those produced by pituitrin, but it increases metabolism, and dextrose and adrenalin together produce an additive effect on the metabolism. In the rabbit the rise of blood sugar produced by injecting dextrose is increased by giving pituitrin simultaneously. Pituitrin raises the blood inorganic P, but dextrose and dihydroxyacetone reduce it; large doses of pituitrin counteract the fall due to the latter, but have less effect on that due to dextrose. It is considered that the effects of pituitrin and adrenalin upon metabolism may be due to alterations in the blood distribution in the body and to increased work of the heart or intestinal muscle, and that it is unnecessary to postulate a direct antagonism between insulin and pituitrin or adrenalin.

Pathogenesis and treatment of endocrine dermatoses in women. Samuel, M. and L. Strauss, Med. Klin. **25**: 1698. 1929.

Employing a modified Bang's micro-method and, in a few instances, checking the results by the method of Hagedorn-Jensen, the authors made fasting blood sugar determinations on 250 cases of pruritus and related dermatoses in women and 40 cases of the type which belong to the domain of ovarian and similar disturbances. In the light of previous work and their own, they have been struck with the apparently very definite association between such diseases and disturbances in carbohydrate metabolism. As a result of the studies in their cases they were led to recognize the occurrence of a form of very slight hyperglycemia, more or less fleeting in character, which appears in otherwise healthy women and girls in the course of pruritic diseases and disturbances in ovarian function. Among the pruritic dermatoses studied they mention pruritus vulvae, with and without disturbances of vaginal secretion, general pruritus, dermatitides, intertriginous eczema of the vulva and anal eczema. Of the 250 cases belonging to this group two-thirds were women in the climacterium and pre-climacterium, and among the remainder of those studied the married women were much in excess of the unmarried. Those women who had borne children constituted the chief contingent with blood sugar increase. Of the 250 pruritus cases 164 showed a more or less marked increase of fasting blood sugar with values ranging from 125 mgm. per cent to 165 mgm. per cent. The pruritus cases at the climacterium showed the greatest incidence of hyperglycemia, with blood sugar values on the average higher than in the young women and girls. As illustrative of the pruritic type of case studied, the authors briefly cite three cases of patients, one, aged 48 with pruritus vulvae, a second, aged 42, preclimacteric, with pruritus, and a third, aged 32, with burning in the vagina and an intensely itching intertriginous eczema. No improvement had resulted in any of the cases under ordinary treatment. The fasting blood sugars in the three cases were, respectively, 156 mgm. per cent, 138 mgm. per cent and 148 mgm. per cent. Treatment in the first instance with a diabetic diet was of no avail. All the cases responded favorably almost immediately after a daily single injection of insulin ranging from 10 to 15 units over periods of 5 to 8 days and thereafter every second day for one or two weeks. This treatment was augmented with a light anti-diabetic diet. In the third case cited the blood sugar fell to 122 mgm. per cent two months after the treatment. About one-half of the women with disturbances of ovarian function and related manifestations showed more or less gross disturbances in carbohydrate metabolism. Hyperglycemia was prominent at the climacterium and also in younger women with menorrhagia and painful menstruation of ovarian dysfunction. Treatment with insulin in these cases resulted in less menstrual bleeding and much subjective relief. The

authors in this connection mention the fact that an increase of blood sugar level has been relatively frequently observed during menstruation and pregnancy, phenomena which would serve to support the assumption that the findings and results in their present group of cases are to be explained on the basis of endocrine interrelationships. They conclude that all these findings point with reasonable certainty toward endocrine relationships between the ovary and carbohydrate metabolism. Samuel and Strauss esteem the practical aspect, as well as a diagnostic support, of their investigations to be the average good effect of small doses of insulin in the diseases under consideration. They claim to have observed even a favorable influence of insulin in cases of pruritus and related dermatoses and also in ovarian dysfunctions, in which the blood sugar was not increased. By their experience, ordinarily, a daily 10 to 15 unit dose of insulin for a few days to a period of 14 days, with a relatively poor carbohydrate diet, suffices to effect the disappearance of the disease manifestations.—M. H. Goodman.

Synthalin-B in diabetes mellitus. Ulrich, H., New England J. M. **202:** 814. 1929.

This drug, a modified synthalin (deca-methylin-diaguanidin), was given by mouth in seven uncomplicated cases of diabetes. There was definite reduction of blood sugar in all cases, unpleasant or toxic symptoms in three. This drug may supplement insulin in certain cases but must be used with caution until its toxic properties are better understood.—J. C. D.

Concerning certain factors which may influence the sugar content of the blood and urine. Watson, E. M., J. Lab. & Clin. Med. **23:** 234. 1929.

The relation between the blood sugar concentration, the hourly output of sugar in the urine, and the reaction of the urine was studied in a series of non-diabetic and in a series of diabetic patients on a standard diet. There appeared to be no constant relationship between the reaction of the urine and the sugar content of the blood and urine except perhaps during the morning. When breakfast was omitted, an increase in the output of sugar in the urine occurred, and in the case of diabetic individuals, there was an obvious rise in the blood sugar as well. This increment accompanied an increase in the alkalinity of the urine. Since the morning alkaline tide of the urine appears to be related to an alteration in the acid-base balance associated with the change from the sleeping to the waking state, the authors suggest that the same process of readjustment may be the factor in causing an increase of the blood and urine sugar during the early part of the day.—I. B.

The clinical syndrome of hyperparathyroidism. Barr, D. P. and H. A. Bulger, Tr. A. Am. Physicians, **44:** 238. 1929.

This is a brief discourse on parathyroid hyperactivity with two illustrative cases. Clinical hyperparathyroidism, a condition resembling the overdosage of parathormone in animals, is associated with hypercalcemia, excessive excretion of calcium in the urine, hypotonia of muscles and a tendency to metastatic calcification. This state occurs most frequently in association with generalized von Recklinghausen's disease, of which it may possibly be the cause. It may occur also as a secondary manifestation in a variety of conditions among which must be included multiple myeloma, a case of which has been reported.—I. B.

The action of parathormone in tetany due to parathyroid extirpation (Die Wirkung des Parathormons bei Tetania parathyreopriva). Elmer, A. W. and M. Schefs, Klin. Wchnschr. **8:** 1404. 1929.

The authors report four cases of tetany following thyroidectomies, treated with parathormone. On comparing the action with calcium preparations and vigantol in these cases, they found that the parathormone was more efficacious and acted with decidedly greater promptness. The dosage varied with the individual case, controlled by blood calcium determinations. Concomitant with the clinical improvement, blood chemistry changes occurred. The phosphorus and blood potassium were lowered. The influence upon the alkali reserve and the coagulation time was not constant. It is recommended that parathormone be used in all cases, especially the acute cases with severe symptoms. In chronic cases, simultaneous peroral calcium administration is advised.—O. O. Meyer.

Hyperparathyroidism (hyperfunction of a parathyroid tumor in a case of generalized osteitis fibrosa). Hunter, D., Proc. Roy. Soc. Med. **23**: 27. 1929. (Sect. Med.).

The patient was a single woman of 41 complaining of pain in the right knee on climbing stairs. The joint was not swollen. Soon there occurred pain in the lower part of the back and the entire left leg. Within 2 years after the onset she was unable to walk without assistance due to pain in the lower spine and right knee. Shortly afterward there occurred a sharp attack of right lumbar pain, increased frequency of micturition and vomiting which subsided within a week. The family history was not significant. Physical examination and a clinical study including radiograms yielded a diagnosis of hyperparathyroidism. The excretion of calcium was found to be equivalent to the continuous administration of about 120 units of parathormone daily. A suspected parathyroid adenoma resulted in operation. It was found that the left inferior parathyroid gland was replaced by a cystic adenoma and this was excised. Two days after the removal of the tumor the calcium and inorganic phosphorus values of the blood were restored almost to normal, and by the fourth day pressure on the bones no longer caused pain. The author concluded that the tumor served as a hyperfunctioning ductless gland which was the primary cause of the bone disease.—I. B.

Pineal syndrome (ocular palsies and precocity) in a boy of 12. Adie, W. J., Proc. Roy. Soc. Med. **23**: 2. 1929. (Sect. Neur.)

The patient was a boy aged 12 who complained of headache, "fits," double vision, and shaking of the right arm, all of one year's duration. Nothing was known of his early history except that at the age of 8 he was "fully developed" and was not permitted to undress before his sisters. His sexual development was that of a young adult. He was intelligent but not precocious in book-learning. He was also an incorrigible thief. He presented, among others, the following signs: Left pupil almost inactive to light; both pupils very sluggish on convergence; upward movements of eyeballs absent; downward movements poor; convergence very poor; coarse tremor of right arm of intention type, and internal hydrocephalus.—I. B.

The treatment of bovine tuberculosis by extracts of spleen (Essai du traitement de la tuberculose, chez les bovidés, par les extraits spleniques). Biélinsky, A. D., Russian J. Endokrinol. **3**: 136. 1929.

Saline extracts of macerated spleen pulp injected into tuberculous cattle caused an attenuation of the response to tuberculine, a quicker resorption of the tuberculous lesions and rapid calcification of the organs attacked. The animals treated showed no increased temperature or other indications that the material was toxic.—M. O. L.

Internal secretions and immunity. II. The effects of ablation of the thyroids and the testes, and of the rate of agglutinin formation in active immunization by the typhoid bacillus (La sécretion interne et l'immunité. II. De l'effect produit par l'ablation de la glande thyroïde, des testicules et de la rate sur la formation des agglutinines dans l'immunisation active par le Bacille de la fièvre typhoïde). Botchkareff, P. V. and E. P. Tchernosatonsky, Russian J. Endokrinol. **3**: 100. 1929.

Ablation of the thyroids or of the testes caused a lessened capacity of formation of antibodies to the typhoid bacillus, and a decrease in the rate of formation of agglutinins.—M. O. L.

Effect of thyroidectomy on the metabolic rate (both basal and maximum) (Influence de la thyroïdectomie sur le métabolisme énergétique [métabolism de base et métabolisme de sommet]). Chahovitch, X., Compt. rend. Soc. de biol. **100**: 1220. 1929.

Removal of the thyroid in rats reduces the basal metabolism as is well known. It reduces also the maximum or summit metabolism as obtained by exposure to intense cold. Exposure to cold is known to be a powerful stimulus for adrenals and thyroid but the author in collaboration with Giaga pointed out that adrenalectomized rats completely lose their heat regulation when

exposed to cold. The conclusion was that the thyroid does not work in this circumstance if the adrenals are removed. The shivering process was not studied by the author though it plays an important role.

The influence of heredity in exophthalmic goitre. Cockayne, E. A., Arch. Dis. Childhood, **3**: 227. 1928.

That the disease is so rarely present at birth, so variable in its date of onset and so often transmitted by apparently healthy parents, are facts which are more easily explained on the basis of an inherited constitutional weakness of the thyroid gland rather than of Graves' disease itself. The constitutional weakness is inherited as a dominant and some of those who inherit it may remain apparently healthy while others may develop any or all signs of the disease under the influence of injurious local geographical influences. The author reports four instances of exophthalmic goitre in one family.

—M. B. G.

Contribution to the study of "precocious matronism" (Contributo allo studio del matronismo precoce di Pende). De Candia, S., Riforma med. **45**: 799. 1929. Abst., Rev. franç. d'endocrinol. **7**: 336.

Pende has described, under the title of "precocious matronism" a new form of infantile obesity which until that time had been confused with cases of infantile adipose myxoedema, or with other adolescent body enlargements. It has to do with children of five to seven years of age at the most, who are rapidly growing fat. The change in shape is of the type usually met with in women of mature age, hence the name matronism. Pende considered this syndrome as resulting from a more or less serious hypothyroidism associated with a cortical hypersuprarenalism causing a precocious maturity of the genital glands. The author reports a case of this type in a young girl five years old. The child had the appearance of an adult. There was excessive body development, the proportions resembling the megalosplanchnic type. There was a relative decrease of calcium excretion with increased elimination of potassium and cholesterin with hyperuricemia and hyperglycemia. The basal metabolism was slightly lowered. The extra fat was very noticeable at the neck, in the region of the ribs, the breasts, the flanks, the belly and the buttock.

—Translated by J. Gagnon.

Further studies of the thyroid gland. V. The thyroid gland as a growth-promoting and form-determining factor in the development of the animal body. Dye, J. A. and G. H. Maughan, Am. J. Anat. **44**: 331. 1929.

Young dogs were used in these experiments, complete litters being employed. Half of the puppies, usually the larger ones, were thyroidectomized when five to six weeks of age; the remaining half were kept as littermate controls. The selection was always made so that the experimental and control animals were of the same sex. A comparison was first made between the thyroidless cretin and its control littermate, as used in a single experiment, then a composite comparative analysis of all animals was made. Careful measurements were taken to record body growth in control and experimental animals. After autopsy the skeletons were prepared and various measurements taken. As a result of their studies the authors conclude that the thyroid gland normally exerts a very marked stimulating influence on the growth impulse of the various parts of the animal body. They find that the retardation of growth following extirpation of the thyroid in young pups does not affect all parts of the body equally. The retardation of the body as a whole is greater than of the skeletal system, and the individual bones are not affected to the same extent in all proportions. In general, the modifications are similar in all bones, viz., an absolute retardation of growth in length, weight and volume and in the epiphyses. Bone growth from endochondral and epiphyseal plate ossification is strikingly retarded, while sub-periosteal and membrane bone formation are little or not at all retarded and may even be accelerated. The oxygen-consuming power of surviving skeletal muscle is reduced to 68.1 per cent of its normal level. Bone growth is affected in the same direction, but with the exception of growth in weight, which is reduced to 68.9 per cent of the normal values, is affected less than that of the "fundamental" tissue metabolism. This is probably due to the lower level of bone metabolism as compared with muscle, viscera, etc.—W. J. A.

Pregnancy complicating simple goitre and Graves' disease. Gardiner-Hill, H., Lancet, **216**: 120. 1929.

An analytical study of histories of twenty-six cases of simple goitre and eighty-nine cases of Graves' disease to determine the incidence and effects of pregnancy. The incidence of pregnancy was average in cases of persistent adolescent goitre but below average in simple goitre appearing in adult life, especially if symptoms of hypothyroidism were present. Pregnancy was followed by increased hypertrophy of thyroid gland and hypothyroidism. Miscarriages were more frequent in the presence of hypothyroidism. When Graves' disease was present the incidence of pregnancy was low, and premature births and miscarriages were more frequent. Conception usually occurred during a remission of the disease. During pregnancy there was usually amelioration of the symptoms of Graves' disease. Persistent improvement after pregnancy terminated was noted more frequently in cases which went to full term. Frequent miscarriage or premature birth may be attributed to shock, mental stress, inadequate rest, for where satisfactory conditions were attained and mental stress was minimized the results were generally good. The number of simple goitres reviewed is too small to justify conclusions. The author states that his findings in Graves' disease differ from the reports of Plummer and others. Dissimilarity of symptoms of goitre according to the locality may account for the variations reported.—J. P. Pratt.

Insulin in the treatment of hyperthyroidism (Insuline dans le traitement de l'hyperthyroidie). Goffin and J. Slosse, Presse mèd. **37**: 440. 1929.

The authors administered insulin in doses as high as 60 units to patients with hyperthyroidism in whom the customary treatment had been ineffectual. The results were followed up for a period of two years. In the majority of these cases there occurred a retardation of the pulse rate, increase in weight, and a lowering of the basal metabolism.—I. B.

Masked hyperthyroidism. Hamburger W. W., Tr. A. Am. Physicians, **44**: 348. 1929.

A series of cases of atypical thyrotoxicosis are presented illustrating the difficulties of diagnosis and the frequency with which disturbances of the thyroid gland masquerade as other disease entities. The cases presented include: a case of persistent grave hyperemesis and dysphagia necessitating nasal feeding; a case of cardiorenal-vascular disease with arterial hypertension and heart failure; a case of supposed severe diabetes mellitus with secondary hypoglycemia following massive insulin injections; a case of long-standing chronic myocarditis of unknown etiology; a case of rheumatic mitral stenosis and insufficiency and aortic insufficiency with paroxysmal auricular tachycardia and unrecognized thyrotoxicosis; a case of angina pectoris with unrecognized substernal goiter, and others. The crucial diagnostic findings are considered to be the presence of a persistently elevated metabolic rate unexplained by other conditions, and the relief of symptoms following iodine medication or thyroidectomy.—I. B.

Structure of the thyroid gland in toxic goiter. Harsha, W. T., M. Clin. North America, **23**: 501. 1929.

This contribution is particularly valuable for its photomicrographs. One feature not usually accentuated in the consideration of thyroid pathology is the lymphatic hyperplasia found in the thyroid in some toxic cases. Central areas of lymphatic hyperplasia are made up of lymphoblasts with many active mitotic figures. The lymphocyte count in some of the more toxic cases is occasionally high—50 to 70 per cent small lymphocytes. In two cases massage of the thyroid gland for 10 minutes resulted in an increase of lymphocytes in the circulating blood. In one case the increase was from 40 per cent prior to massage to 78 per cent 6 hours later. In the other case in which massage was attempted, the increase was from 57 to 62 per cent. No control by massage elsewhere was made. In one case of toxic goiter the basal metabolism was increased from plus 46 per cent prior to massage to plus 80 per cent following a 15-minute manipulation of the thyroid gland after 6 hours, and it required 36 hours for the B.M.R. to reach plus 50 again. In two other cases there was no increase in the basal metabolism following massage.—I. B.

An etiological study of primary Graves' disease with special reference to the significance of the sex events of the female. Hill, H. G., Quart. J. Med. **22**: 217. 1929.

This paper is a valuable contribution serving to emphasize the causal relationship of psychic trauma and sex epochs in Graves' disease. Two hundred and six cases of primary Graves' disease were studied. Of these cases, 183 were females and 23 males, a ratio of 8:1. Of the 183 females, 32 were adolescent, 63 single, and 88 married women. Of the males, 6 were adolescent, 4 single, and 13 married men. The incidence of the disease was almost entirely limited to the period of active sex life, only one case occurring before puberty and only 5 after the climacteric. In 80% of these cases the disease was precipitated by extrinsic factors, shock, mental stress, and sepsis. In 50% the 2 former factors, in 20% the latter, whilst in 10% they were combined. In the remaining 20% there was no apparent extrinsic exciting factor. The sex events in the female—puberty, pregnancy, the puerperium, and the climacteric—appear to be important predisposing factors, for the incidence of cases was considerably greater at these times. 56.6% of the adolescent and 76.2% of the climacteric cases developed the disease within 3 years of these events. Of the 71 cases in married women during the child-bearing period, 41 developed the disease during pregnancy, the puerperium, or after miscarriage. The incidence during the puerperium was double that during pregnancy. Of the 71 cases in married women during the child-bearing period, 14, or 19.7%, had had no pregnancy prior to the onset of the disease; 13, or 18.3%, had had only 1 pregnancy; and 15, or 21.1%, developed the disease during their first pregnancy or puerperium. Of the 21 climacteric cases, 17 were married and 4 single. Seventy-two per cent of the former had had 2 or more pregnancies. The low incidence of cases at the climacteric in single women is in keeping with the general decrease in incidence in single women in later life.—I. B.

The ovary in experimental hypo- and hyper-thyroidism. II. The influence of experimental hyperthyroidism on gestation. Kunde, M. M., A. J. Carlson and T. Proud, Am. J. Physiol. **88**: 747. 1929.

Cretin rabbits were produced by the removal of the thyroid at the age of three weeks and the animals were allowed to remain in the cretin stage for several months. They were then fed desiccated thyroid until symptoms of hyperthyroidism resulted, and then sacrificed. Histological section of the ovaries revealed a large number of primary follicles and apparently normal Graafian follicles in all stages of development. In rabbits with severe hyperthyroidism thus experimentally produced, the processes of oestrus, ovulation, fertilization, migration and implantation take place, but in most instances the young are never born, resorption occurring instead. Resorption of all or many of the fetuses occurs during the latter two-thirds of the pregnancy.
—M. B. G.

Further observations on latent hyperthyroidism masked as heart disease: angina pectoris. Levine, S. A. and G. L. Walker, New England J. M. **202**: 1021. 1929.

A general discussion is followed by eleven brief case histories. The presenting symptoms are those of cardiac disease. Exophthalmos and enlargement of the thyroid are absent, but tremor, sweating, a feeling of warmth, together with loss of weight and attacks of diarrhea, are suggestive. The skin tends to be warm, moist, and pigmented, and to have a peculiar salmon color. The patient is more nervous and alert than one would expect him to be with such a degree of illness. These conditions suggest the diagnosis of hyperthyroidism, which must, however, be confirmed by a study of the basal metabolism. In such cases proper surgical intervention yields very satisfactory results.
—J. C. D.

Specimens from a case of malignant goiter. Moncrieff, A., Proc. Roy. Soc. Med. **23**: 1. 1929. (Sect. Dis. Child.).

The patient was a girl aged 11 years. There was no family history of goiter. Swelling of the neck was first noticed at the age of 4. She had lived in Scotland most of her life except for a trip to Australia. For the few months previous to her admission to the hospital there had been increasing noisiness in respiration and the thyroid had become larger. Adenomatous goiter was

diagnosed but thyroidectomy proved to be very difficult owing to adhesions, especially of the deeper portions of the gland. The child succumbed 12 hours after the operation. Only a limited examination of the operation area was permitted, but it was then found that the deeper portions of the gland were very hard and were adherent to the deeper structures of the neck. In one place the trachea was infiltrated with growth which protruded through, just below the larynx. Microscopical examination of the superficial portions of the gland showed a parenchymatous type of goiter, while in the deeper portions malignant changes were observed.—I. B.

Hyperthyroidism associated with abdominal lesion. Priest, W. S., M. Clin. North America, **13**: 483. 1929.

This contribution is essentially a discourse on two illustrative cases of so-called hyperthyroidism associated with abdominal lesions, and a discussion on causal relationship. In one of these cases the abdominal condition was in the nature of a low-grade infection; in the other there was a primary carcinoma of the head with possible abdominal metastases.—I. B.

Roentgentherapy of Graves' disease and its dangers (Die Roentgentherapie der Basedowkrankheit und Ihre Gefahren). Rahm, H., Klin. Wchnschr. **24**: 1131. 1929. Abst., Arch. Physical Therapy, **11**: 44.

It is out of the question to consider roentgenotherapy in exophthalmic goiter as not dangerous. A great many deaths have been described, partly due to the hyperthyreotic response following irradiation, partly to lesions of the larynx. Another danger is given by the possibility of Graves' disease being converted into myxoedema. A further source of danger is the fact that roentgenotherapy may hamper the timely chance that operation would afford. Preoperative roentgenotherapy is not without dangers, unless basal metabolism be controlled.

Effects of combined administration of extracts of anterior lobe of pituitary and of potassium iodide on thyroid gland. Silderberg, M., Proc. Soc. Exper. Biol. & Med. **27**: 166. 1929.

Fourteen guinea pigs were fed KI daily in doses of .05 or 0.1 grams. From the tenth to the seventeenth days, 10 of the pigs were given daily intraperitoneal injections of 1cc. of an acid extract of anterior pituitary substance. Both the KI and the pituitary extract exerted their specific effects on the thyroid gland, not in summation but in separate areas, giving a mosaic of areas in which one or the other effect predominated. The typical effect of the anterior lobe extracts was to cause hypertrophic acinus cells, absorption of the greater part of the colloid and irregular acini. The KI effects were a considerable increase in mitoses, a slight increase in the size of the cells and a slight softening of the colloid.—M. O. L.

Modifications of the precipitation of erythrocytes with respect to the condition of the thyroid (Modifications de la reaction de precipitation des erythrocytes en rapport avec le fonctionnement de la thyroïde). Tchernosatonsky, E. P., Russian J. Endokrinol. **3**: 126. 1929.

The sedimentation velocity of the erythrocytes was studied in 146 sheep and 14 rabbits before and after thyroidectomy and after the administration of thyroid substance, and in 27 patients with thyroid disorders. In the sheep, the sedimentation rate was between 3 and 11 mm. per hour and in the rabbit 3 to 6 mm. per hour. After thyroidectomy, the sedimentation rate decreased, being slowest 4-6 weeks after the operation. In the sheep, the administration of dried thyroid substance in doses of 0.02-0.06 grams per kgm. caused a marked increase in the sedimentation velocity. The administration of iodine in the form of Lugol's solution also caused an accelerated sedimentation rate, but less marked than thyroid substance. The sedimentation rate appears to be increased in patients with hyperthyroidism and decreased in patients with hypothyroidism, and the author believes that this is of diagnostic value.

—M. O. L.

The influence of the thyroid gland on the circulatory blood volume and the blood depot of the organism (Der Einfluss Der Schilddrüse Auf Die Zirkulierende Blutmenge und Die Blutdepots Des Organismus). Preliminary Report. Wislicki, L., Klin. Wchnschr. **8**: 1568. 1929.

Wislicki says that in Basedow's disease, through the increase of basal metabolism, there is a definite increase of the minute volume of the blood. In contrast the opposite is found in myxedema and obesity. Noting this difference in the blood volume in hyperthyroidism and myxedema, Wislicki studied the blood volume of hyperthyroid cases. He used the Trypan red method of Seyderhelm and Lampe and the blood estimation was taken after rest in bed and at least three and one-half hours after breakfast. In healthy individuals the plasma volume was 38-45 cc. per kgm. The question arose whether the increase of the blood volume in Basedow's disease was a non-specific reaction of the organism in response to the increased circulation or if it was a specific reaction of the thyroid gland. He therefore gave thyroid medication to see its influence on the circulating blood volume. In cases of obesity it was shown that the blood volume increased by the giving of thyroid extract, the patient lost weight but at the same time the metabolism increased. In cases in which the medication produced palpitation of the heart without achieving the increase in basal metabolism, it was noted that there was no influence on the blood volume. In myxedema after thyroid medication, the blood volume increased one to one and one-half times. Wislicki experimented on thyroidless animals in which the carbon dioxide was artificially increased in the circulation. He was unable to demonstrate any carbon dioxide in the spleen. The blood channels of the spleen apparently remained closed after thyroidectomy. The longer the time between the thyroid extirpation and the experiments, the greater the amount of carbon dioxide could be introduced in the blood without producing carbon dioxide in the spleen. The addition of thyreiodin or thyroxin opened up the channels in the spleen so that a normal reaction was obtained. Therefore, we can say that the thyroid has a function which influences the blood depot.—R. C. Moehlig.

The incidence of goiter among adults in Nashville, Tennessee. Youmans, J. B., South. M. J. **22**: 966. 1929.

Eighty-five goiters were found among 500 adult colored and white patients of both sexes, a total incidence of 17%. A much higher incidence was found in women at certain age periods, the maximum (42%) occurring in white women during the fifth decade. The total incidence was about four times greater in women than in men, and was slightly less among colored than among white patients. Both white and colored women showed an increasing incidence with advancing age up to a maximum at the fifth and sixth decades, respectively. Men showed a maximum incidence during the second and third decades with a sharp drop thereafter, and a secondary rise in the colored men at 40 to 49. The occurrence of goiter in this locality may probably be attributed in part to primary iodin deficiency, although sufficient data in regard to the iodin supply of the region is not available to determine this definitely. It is suggested that improper diet and poor hygienic conditions may be additional factors of etiologic importance in the group studied.—Author's Summary.